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## SUPERNORMAL CIRCULATION IN RESTING SUBJECTS (HYPERKINEMIA)

WITH A STUDY OF THE RELATION OF KINEMIC ABNORMALITIES  
TO THE BASAL METABOLIC RATE

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AND

LEON JONAS, M D \*

PHILADELPHIA

During the past fifteen years, estimations of basal, or resting, cardiac output, first by the ethyl iodide method and later by the ballistocardiogram, have been made for about 1,400 subjects. In this work we had both immediate and remote objectives in view. The first of the latter was attained when we secured 100 subjects with subnormal circulation and discussed the clinical significance of the abnormality<sup>1</sup>. It has taken us three years longer to assemble data on 100 subjects with circulation above the normal, and a chief feature of this report is an account of this group.

In addition, using all our data, we have studied the relation between abnormalities of the amount of the resting circulation and of the basal metabolic rate.

By our studies important abnormalities have been demonstrated in many patients who have had symptoms referable to their circulation without detected organic disease. As these abnormalities seem fundamental to an understanding of the group, cases in which they occurred will be given special emphasis.

### METHODS

The technics used have been reported in detail,<sup>2</sup> and their description need not be repeated. We do not regard methods for determining car-

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\* Woodward Fellow in Physiological Chemistry

The completion of this work was aided by a grant from the Daland Fund of the American Philosophical Society.

From the Research Department of Therapeutics, the William Pepper Laboratory of Clinical Medicine, and the Medical Division of the Hospital of the University of Pennsylvania.

1 Starr, I, and Jonas, L. Syndrome of Subnormal Circulation in Ambulatory Patients, Arch Int Med 66 1095-1111 (Nov) 1940

(Footnotes continued on next page)

diac output as highly accurate, but they are certainly accurate enough for the present purpose, to divide clinical patients into three groups, with circulation normal, above normal and below normal

All tests were made with the subject supine and after a rest period of fifteen minutes or longer. At first all estimations of cardiac output were performed before breakfast, in recent years they have been performed during the morning or afternoon, two hours or more after a light meal

Our normal standards have been published<sup>3</sup>. In their calculation Suter's autopsy data on aortic size were employed as a factor in the estimations of cardiac output by the ballistocardiogram. The use of this factor has been criticized and strong evidence obtained that the aorta in living persons is larger than our estimate of it<sup>4</sup>. To correct for this error would raise the calculated cardiac output about 20 per cent. But in the past our estimations of the circulation of patients have usually been recorded as percentage derivations from the expected normal and we plan to continue this method. The results would not be changed by employing the correction suggested by Cournand and associates, as both normal and abnormal values would be raised proportionately

The boundaries of the normal zone are 22 per cent from the mean. The result of each method has been judged by its own standard, and both will be expressed in deviation from the normal in percentage. Thus all patients included in this series had circulations which exceeded the expected normal for their weight by 23 per cent or more

Of our 100 patients, the estimation was made for 25 by the ethyl iodide method and for the remainder by the ballistocardiogram. Typical records of the latter are shown in figure 1. The great majority of the conclusions in this paper can be justified by results obtained by both methods

When the ethyl iodide method was in use, prior to 1936, estimations of basal metabolic rate were made simultaneously with estimations of

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2 (a) Starr, I, Jr, Collins, L. H., and Wood, F. C. Studies on the Basal Work and Output of the Heart in Clinical Conditions, *J Clin Investigation* **13** 13-43 (Jan) 1933. (b) Starr, I., Rawson, A. J., Schroeder, H. A., and Joseph, N. R. Studies on the Estimation of Cardiac Output in Man, and of Abnormalities of Cardiac Function, from the Heart's Recoil and the Blood's Impacts. The Ballistocardiogram, *Am J Physiol* **127** 1-28 (Aug) 1939. (c) Starr, I., and Rawson, A. J. The Vertical Ballistocardiograph. Experiments on the Changes in the Circulation on Arising, with a Further Study of Ballistic Theory, *ibid* **134** 403-425 (Sept) 1941.

3 Starr, I., and Schroeder, H. A. The Ballistocardiogram. II. Normal Standards, Abnormalities Commonly Found in Diseases of Heart and Circulation and Their Significance, *J Clin Investigation* **19** 437-450 (May) 1940.

4 Cournand, A., Ranges, H. A., and Riley, R. L. Comparison of Results of the Normal Ballistocardiogram and a Direct Fick Method in Measuring the Cardiac Output in Man, *J Clin Investigation* **21** 287-294 (May) 1942.

cardiac output In recent years the two tests have not been made simultaneously, but always within a few days of each other. Also, the basal metabolic rate has not been estimated in every case Data on this rate are available for only 55 of the 100 patients with circulation exceeding the normal

The absolute amount of cardiac output is meaningless without knowledge of the size of the subject Estimations of basal metabolic rate are related to the body surface for a good physiologic reason, for heat is lost from the surface of the body Many authors similarly refer the cardiac output to body surface, although this reason does not apply with the same force, for the elimination of heat is only one of many functions of the circulation In our data<sup>3</sup> the normal subgroup is more homogeneous when the cardiac output is referred to body weight, and so we report our results in terms of weight

One must consider using ideal<sup>5</sup> rather than actual weight One can argue that variation in the weight of any patient depends in large part on difference in the amount of fatty tissue Fat has so small a blood supply that alterations in its amount would affect the magnitude of the circulation very little, a viewpoint supported by our results in emaciated persons This conception raises the question, Would not a better normal standard be achieved by expressing the amount of the circulation in terms of ideal weight rather than of actual weight? If ideal weight is used, our series of patients with hyperkinemia becomes much smaller, only 54 of the 100 having a circulation above normal in terms of their ideal weight

We see only one way to decide such a question and that is in terms of utility Our procedure has been influenced by experience with the estimation of basal metabolic rate Fat also has a low metabolic requirement, but the accepted procedure is to estimate metabolic rate in terms of actual, not ideal surface area, and the present standards have proved useful If the ideal value is used, many subjects now judged abnormal are found to be within the normal range This analogy, together with the uncertainties inherent in estimating ideal weight correctly, have inclined us to use actual weight until data concerning utility can determine which is better

As in the previous investigation, many persons other than ourselves have contributed to the data used, and their names have appeared in previous publications<sup>6</sup> The estimations of circulation were always

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5 Davenport, C B Body Build and Its Inheritance, publication 329, Carnegie Institute of Washington, 1923 McLester, J S Nutrition and Diet in Health and Disease, Philadelphia, W B Saunders Company, 1939

6 (a) Starr, Collins and Wood<sup>2a</sup> (b) Starr, I, Donal, J S, Jr, Margolies, A, Collins, L H, and Gamble, C J Studies of the Heart and Circulation in Disease Estimations of Basal Cardiac Output, Metabolism, Heart Size and



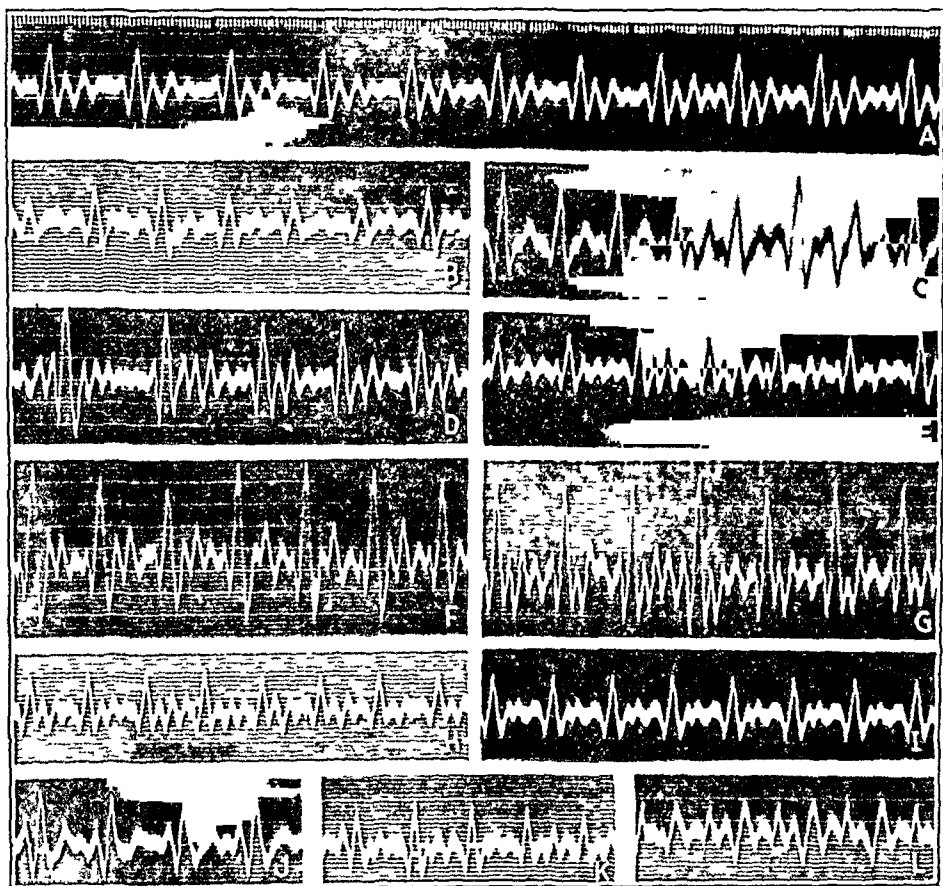


Fig 1—Ballistocardiograms (one-half actual size) of 1 normal subject and 9 patients with hyperkinemia. The time record at the top applies to all, the largest interval being one second. In comparing these records by inspection one must remember that, while the size of the major deflections is related to the absolute amount of the cardiac output, the decision concerning normality depends on this output related to the patient's weight. Also, allowance must be made for the subject's age, for older persons, even though healthy, tend to have smaller impacts than their juniors.

*A*, record of *E D*, a woman aged 21, 5 feet 7 inches (170.2 cm) in height and weighing 140 pounds (63.5 Kg). A normal person, she had a circulation which did not deviate from the normal average.

*B*, record showing the effect of fever. The patient, *R B*, a man aged 40, was 5 feet 5 inches (165.1 cm) in height and weighed 135 pounds (61.2 Kg). He had gonorrheal arthritis, his temperature being 98.4 F. His circulation deviated from the expected normal by +17 per cent, the normal limits being  $\pm 22$  per cent.

*C*, record of the same patient after he had received an injection of killed typhoid bacilli. His temperature was 103.2 F. His circulation was +79 per cent.

(Legend continued on next page)

Blood Pressure in Two Hundred and Thirty-Five Subjects, *J Clin Investigation* **13** 561-592 (July) 1934. (c) Starr, I., Gamble, C. J., Margolies, A., Donal, J. S., Jr., Joseph, N. R., and Eagle, E. A Clinical Study of the Action of Ten Commonly Used Drugs on Cardiac Output, Work and Size. On Respiration, on Metabolic Rate, and on the Electrocardiogram, *ibid* **16** 799-823 (Sept) 1937.

## EXPLANATION OF FIGURE 1—CONTINUED

*D*, record of E K, a boy aged 14, 5 feet 3 inches (160 cm) in height and weighing 91 pounds (41.3 Kg). The systolic blood pressure was 130, and the sounds could be heard at zero pressure. There was clinical evidence of patency of the ductus arteriosus. Our estimate of the amount of the circulation was handicapped by lack of data on the aortic size in children, but the impacts were much larger than we have ever seen in boys of similar age and weight. *E*, record of the same boy seven weeks after successful ligation of the ductus by Dr John B. Flick at the Pennsylvania Hospital. The blood pressure was 106 systolic and 65 diastolic in millimeters of mercury. The diastolic murmur had disappeared, and the circulation had diminished by 24 per cent.

*F*, record of J D, a man aged 25, 5 feet 11 inches (180.3 cm) in height and weighing 148 pounds (67.1 Kg). The basal metabolic rate was +14 per cent and the circulation +57 per cent. This patient, with essential hyperkinemia, is further described in the text (case 6).

*G*, record of H W, a man of 36, 5 feet 6 inches (167.6 cm) in height and weighing 112 pounds (50.8 Kg). There was thyrotoxicosis with a diffuse goiter. The basal metabolic rate was obtained with much difficulty, the patient not tolerating the mouth piece well. Repeated attempts were made, the lowest value believed possible was +66 per cent. The circulation was +109 per cent.

*H*, record of A K, a woman of 18, 5 feet 5 inches (165.1 cm) in height, who came to the hospital weighing 71 pounds (32.2 Kg). There was anorexia nervosa. On admission she was weak. The circulation did not deviate from the normal in relation to her weight at that time. The basal metabolic rate was -27 per cent. After forced feeding for three weeks she had gained 11 pounds (5 Kg) and had become much stronger, the record shown was taken at that time. The circulation was +52 per cent if related to her actual weight, but only +4 per cent when related to her ideal weight, 120 pounds (54.4 Kg). As she further improved the circulation returned to normal.

*I*, record of S P, a woman of 27, 5 feet 3 inches (160 cm) in height and weighing 101½ pounds (45.9 Kg). The basal metabolic rate was -2 per cent and the circulation +35 per cent. This case of essential hyperkinemia is further described in the text (case 7).

*J*, record of A T, a man aged 33, 5 feet 6 inches (167.6 cm) in height and weighing 121 pounds (54.9 Kg). Repeated estimations of the basal metabolic rate gave normal results, the circulation was +57 per cent. This case is further described in the text (case 1).

*K*, record of V D, a woman of 41, 5 feet (152.4 cm) tall and weighing 100 pounds (45.4 Kg). Three months before the test the entire right lung had been removed by Dr Julian Johnson because of lung abscess. A thoracoplasty had been performed two weeks before. There was no fever, the pulse rate was 118. The circulation was calculated to be +66 per cent, but because of the displacement of the heart it was probably somewhat larger.

*L*, record of M N, a man aged 47, 5 feet 7 inches (170.1 cm) in height and weighing 160 pounds (72.6 Kg). The blood pressure was 115 systolic and 92 diastolic. Six months before the test the entire left lung had been removed because of carcinoma by Dr Julian Johnson. While the patient was convalescent from the operation the pulse rate was 125 and the form of the ballistocardiogram somewhat abnormal. At that time the circulation was calculated to exceed +80 per cent. When the present record was taken the form had returned to normal during systole but an abnormal impact was present in diastole. The circulation exceeded +30 per cent.

supervised by Stann, and those of basal metabolic rate have been performed since 1936 by Jonas. Members of the Robinette Foundation, especially Drs M M Livezey, J Edeikin and W A Jeffers, made and interpreted the electrocardiograms and orthodiagrams which we have used.

*Source of Cases*—Most subjects were resident patients or outpatients at the Hospital of the University of Pennsylvania, 2 were from the Pennsylvania Hospital. Rare instances of supernormal circulation were found among about 400 healthy persons: medical students, physicians and hospital technicians tested during various investigations and class demonstrations.

Not all types of patients have been studied. Those too ill to be moved were not tested. We have had a limited experience with the acute febrile diseases, partly because our clinic contains few patients with such diseases and partly because precautions against infection made it more difficult to test them. When working with the ethyl iodide method we distrusted the results in cases in which the lungs were abnormal and avoided such cases. In cases in which blood regurgitates through leaking heart valves, the ballistocardiogram indicates the total cardiac output rather than the amount which contributes to the circulation, so we have omitted such cases from this series. In extreme tachycardia the ballistic after-vibrations may interfere with the record of the following systole. When this occurred the case was omitted. With these exceptions our cases represent a fair cross section of the population of the medical ward with symptoms referred to the heart or the circulation, with the addition of certain interesting cases selected from the surgical wards.

*Terminology*—The term "cardiac output" has always been employed to mean the output from one side of the heart. With reference to the normal state and to most conditions of disease this term is perfectly satisfactory, for the blood expelled from each side of the heart equals the amount of the systemic and also the pulmonary circulation. Therefore the gas methods, which measure the blood flow through the lungs, and the ballistocardiogram, which is chiefly influenced by movement in the aorta, should yield the same result, and both have the right to call their result the cardiac output.

But in certain clinical conditions this agreement does not hold. For example, in aortic regurgitation, the left cardiac output exceeds the right, only the latter equals the systemic and the pulmonary circulations. In patent ductus arteriosus the situation is even more confused, the left cardiac output is larger than the right, but the pulmonary circulation is larger than the systemic, for the left cardiac output equals, not the systemic, but the pulmonary circulation, while it is the right cardiac output which equals the systemic circulation. To use the term

“cardiac output” under such conditions without explanation is to invite confusion of thought

Therefore we prefer to emphasize the “amount of the circulation,” by which we mean the systemic circulation. This term permits no confusion throughout the clinical field, and it places the emphasis on the amount of blood available to supply the needs of the body organs.

In a previous communication we used the term “subnormal circulation” to indicate circulation below the lower normal limit. This term seemed perfectly satisfactory, but the corresponding term, “supernormal circulation,” is more awkward, and the adjective form, as in “supernormal circulatory state,” is even worse. The discovery of a more satisfactory term was not easy. “Supercirculation” smacks unpleasantly of Hollywood, while “hypercirculation,” of mixed parentage, derives dignity only from association with its half-brother, “hypertension,” which has certainly made its place in the English language in spite of carrying a bar sinister. Among the derivations from Greek roots, “hyperrrheaemia” requires too much effort to pronounce differently from the familiar, and very different, “hyperemia.” “Hyperkinemia,” easy to pronounce and with an even shorter adjective, is the best term we have found, Dr. J. H. Austin suggested it.

We propose, therefore, to use the terms hyperkinemia and hypokinemia to indicate the corresponding abnormalities in the amount of the systemic circulation of resting subjects.

## RESULTS

*Patients with Hyperkinemia Considered as a Group*—Sex. Of the patients, 57 were males and 43 were females. The small disproportion is probably due to two facts. One of us (I. S.) selected the patients for study, and in recent years his terms of service in the men’s ward have exceeded those in the women’s ward. Also, he preferred to study the patients of whom he was in charge.

Age. The distribution of the group is shown in figure 2. The subjects tended to be somewhat younger than those with hypokinemia,<sup>1</sup> but the range spread throughout life.

Habitus. There is a distinct tendency for patients with hyperkinemia to be underweight. The deviation from the ideal weight, a figure calculated from actuarial data and based on the subject’s age and height, is given in figure 2. Only 20 of the 100 patients were over their ideal weight. Patients from 21 to 25 pounds (from 9 to 11 Kg.) underweight were found with the greatest frequency.

History. The histories gave no positive information which would enable one to suspect hyperkinemia. As might have been expected from common experience with the increased circulation present during exercise or excitement, palpitation was the group’s most common symp-

tom, but for only 31 patients was it recorded as abnormal. Found so frequently in patients without increased circulation who suffer from hypertension or cardiac disease, and also occasionally in healthy young adults, this symptom is of little help in identifying the magnitude of the circulation.

We also studied the frequency of excessive dyspnea on exertion, weakness, nervousness and tremor. When present these symptoms

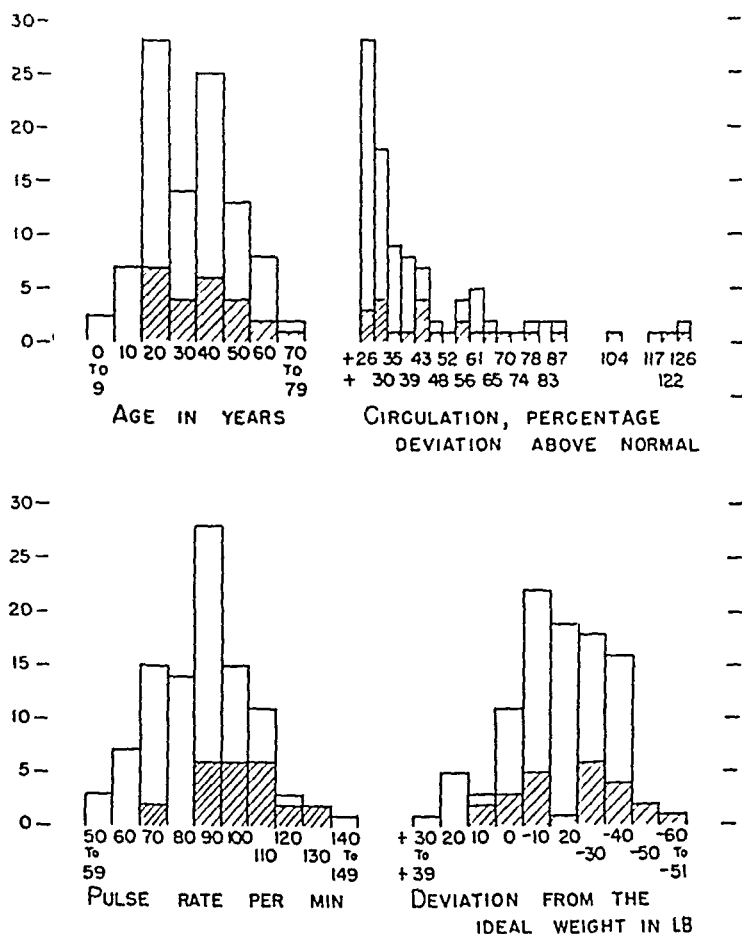


Fig 2—Frequency diagram from data on patients with hyperkinemia. The cross-hatched areas indicate data obtained from the patients with hyperthyroidism in our series.

could usually be accounted for by the major disease from which the patient suffered, and we found no reason to consider them characteristic of hyperkinemia.

**Physical Examination.** This likewise gave no conclusive evidence of the condition. Our data on the pulse rate are given in figure 2, where it will be seen that there was a tendency for the rate to be high, values in the 90's being found most frequently. But hyperkinemia may be present with either tachycardia or bradycardia.

The pulse volume, in reality a pressure difference unrelated to blood flow, showed nothing characteristic

The blood pressure was normal in the great majority of the patients. A few in the series had true hypertension, and a large pulse pressure was found in patients with arteriovenous communications and in some with hyperthyroidism. These were the only abnormalities found.

**Special Tests** Electrocardiograms, estimations of basal metabolic rate and fluoroscopic examinations of the heart were made for many patients. Abnormalities were encountered in some patients, but they were always characteristic of the primary disease, such as advanced heart disease or thyrotoxicosis, so these results will be discussed in connection with the appropriate subgroups. In other patients these

TABLE 1—*Clinical Classification and Frequency of Hyperkinemia*

Group	Total Number of Patients Tested	Number with Hyperkinemia	Percentage with Hyperkinemia
Healthy persons	400	16	4
Patients with hyperthyroidism without obvious cardiac involvement	27	24	89
Patients with emaciation without disease of heart or circulation	12	9	75
Patients with abnormal intercirculatory communi- cations			
Patent ductus arteriosus	7	6	86
Peripheral arteriovenous communications	4	1	25
Patients with anemia	21	5	24
Patients with febrile disease	8	1	12
Patients with hypertension	150	6	4
Patients with pulmonary conditions			
Postpneumectomy . . .	5	4	80
Pulmonary disease . . .	12	3	25
Patients with other conditions (miscellaneous group)	Approx- imately 900	7	1
Patients with essential hyperkinemia		17	

tests gave normal results, and we found nothing characteristic of hyperkinemia itself.

In short, besides the knowledge that hyperkinemia is likely to occur in persons who are underweight and have some elevation of the resting pulse rate, nothing has been discovered which permits one to identify it from the history, the physical examination or routine laboratory tests.

*The Subdivisions of Hyperkinemia*—Table 1 shows our patients with hyperkinemia subdivided according to diagnosis. It also shows the proportion of such patients to the total number of similar subjects we have examined. Some comment is necessary.

Hyperkinemia is found occasionally in healthy persons. Sometimes it was discovered in class demonstrations and was undoubtedly due to excitement, but in large part its observation is to be attributed to an accidental summation of errors. In work with methods which contain

errors there will always be some overlapping of normal and abnormal groups

Almost all of our patients with hyperthyroidism without evident cardiac involvement had hyperkinemia, and the presence of this abnormality has been reported frequently<sup>7</sup>

The emaciated subgroup contained 4 young women in whom no organic abnormality was demonstrated by the hospital study, and their data are given in table 2. The other 5 emaciated patients showing

TABLE 2—Amount of the Circulation Related to Actual Weight of 4 Young Women with Anorexia Nervosa

Patient, Age and Height	Date	Weight, Pounds	Blood Pressure, Mm of Mercury	Circu- lation, Percentage from Normal	Pulse Rate	Basal Metabolic Rate, Percentage from Normal	Comment
A. K., 17 5' 7"	10/21	71	90/64	0	77	-27	Patient very weak, hemoglobin content 84%
	10/23					-23	
	11/14	82	110/60	+52	108		Much stronger
	11/21					-5	
	11/22	88	110/60	+4	98		Anemic, hemoglobin content 56%
M. B., 20 5' 1½"	4/11	73	108/60	-17	62		Second admission
	3/21					+8	
	3/26	74	120/70	+39	98		
H. P., 21 5' 4"	3/28					-8	
	4/22	93	112/72	+43	100	-14	
	11/1					-40	
R. B., 22 5' 2"	11/7	57	80/58	+26	63		
	11/10	60	78/54	+9	65		
	12/9					-18	
	12/16					-18	
	12/24	75	86/60	-9	58		
	1/3					-25	

hyperkinemia had lost from 42 to 22 pounds (19 to 10 Kg.) because of peptic ulcer or prolonged infectious disease.

However, not all emaciated patients show hyperkinemia. We have records of 6 such patients in whom its absence could be attributed to

7 (a) Liljestrand, G., and Stenstrom, N. Clinical Studies on the Work of Heart During Rest. I. Blood Flow and Blood Pressure in Exophthalmic Goiter, *Acta med. Scandinav.* **63**: 99-129, 1925. (b) Fullerton, C. W., and Harrop, G. A., Jr. The Cardiac Output in Hyperthyroidism, *Bull. Johns Hopkins Hosp.* **46**: 203-216 (Feb.) 1930. (c) Boothby, W., and Rynearson, C. H. Increase in Circulation Rate Produced by Exophthalmic Goiter, *Arch. Int. Med.* **55**: 547-557 (April) 1935. (d) Lequime, J. Le debit cardiaque, etudes experimentales et cliniques, Paris, Masson & Cie, 1940.

advanced heart disease or hypertension. But there were 3 other patients, 48, 35 and 27 pounds (22, 16 and 12 Kg) underweight, who had normal circulation without any obvious reason. Indeed, the diagnosis of hyperkinemia in the presence of emaciation is largely a matter of definition, and this fact has been discussed.

Attention was directed to the subgroup with pulmonary disease by the finding of hyperkinemia in 4 of 5 patients tested from two weeks to six months after the surgical removal of one lung. These patients had resting pulse rates of 125, 118, 112 and 95. The presence of pronounced cardiac displacement would cause an error in estimating the circulation by ballistocardiogram, but its direction indicates that the circulation was even larger than our estimate of it.

In other patients with pulmonary disease, hyperkinemia has been found infrequently. Most patients with advanced diffuse pulmonary fibrosis from silicosis or infection have had normal or subnormal circulation.

In association with hypertension, hyperkinemia has been found only rarely, but the 6 patients with this combination had a great deal in common. One had glomerulonephritis and the other 5 essential hypertension. The highest blood pressure was 250 systolic and 137 diastolic and the lowest 156 systolic and 112 diastolic. All but 1 had great cardiac enlargement, the silhouette areas ranging from +118 to +47 per cent from the expected normal, while the heart of the last was top normal in size. All these patients were extremely ill and suffering from cardiac or cerebral manifestations. Three died within a month, and the remainder were discharged in such poor condition that prolonged life seemed most unlikely. Apparently hyperkinemia is found associated with hypertension only as a terminal condition, so we have no evidence that the increased circulation is a factor in the genesis of hypertension.

When patients with abnormal intercirculatory communications are studied there are errors in estimating cardiac output by any method.<sup>8</sup> The ballistocardiogram overestimates the amount of the circulation in this condition, but theoretic considerations led to the expectation that the error would be too small to account for the large abnormalities found in most of these patients.

Some of our patients in this subgroup were children, and special difficulties affected the interpretation of results. The lack of data on aortic size in children prevents estimation of the absolute amount of circulation but does not hinder the detection of changes in individual patients. Also, we have tested few normal children. But the children included in this study gave impacts so much larger than healthy controls

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<sup>8</sup> Keys, A. Estimation by the Foreign Gas Method of the Net (Systemic) Cardiac Output in Conditions Where There Is Recirculation Through the Lungs. *Am J Physiol* **134** 268-280 (Sept) 1941



that we have not hesitated to include them among the subjects with hyperkinemia

Of the 8 patients with hyperkinemia in this subgroup, in 6 there was patent ductus arteriosus, the diagnosis being proved at operation for 5. In 1 of the remainder there was a traumatic arteriovenous communication of the occiput, in the other, an interventricular septal defect, demonstrated much later at necropsy. The 4 patients without hyperkinemia included 1 with patent ductus arteriosus proved at an operation which he did not survive. In 2 there was a traumatic arteriovenous communication in the leg and in 1 a congenital hemangioma of the leg. In the last 3 patients small changes in blood pressure, pulse and circulation on occlusion of the vessels of the affected leg indicated that the communications were small ones.

After ligation of the ductus the change in the circulation was usually striking. The records of 1 patient are shown in figure 1. In addition, in an adult operated on by Dr. John B. Flick, the circulation diminished from +65 to +4 per cent. In 3 children operated on by Dr. Julian Johnson, it diminished by 35, 24 and 10 per cent, respectively. These results are similar to those of Eppinger, Burwell and Gross.<sup>9</sup>

The infrequency of hyperkinemia in association with the febrile diseases was unexpected. Although an increase in the circulation after the artificial induction of fever has been demonstrated repeatedly<sup>10</sup> (an example is shown in figure 1), we found hyperkinemia in only 1 of 8 patients tested during a febrile disease. This patient had a temperature of 100.6 F from phlebitis. In 7 other patients with the temperature between 101 and 104 F, tested during typhoid fever, lobar pneumonia, rheumatic fever or tuberculosis, normal circulation was found. Our data are few, but they suggest that hyperkinemia will be found in the sthenic, not in the asthenic, phase of the febrile diseases. Perhaps these findings are a demonstration of the old view which recognized a difference between the circulation in the sthenic and the asthenic stages of fever and served as the basis for such practices as bleeding early, but never late, in the course.

Also, among patients with anemia the number with hyperkinemia was smaller than the literature had led us to expect.<sup>11</sup> In each of 5

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9 Eppinger, E. C., Burwell, C. S., and Gross, R. E. The Effects of Patent Ductus Arteriosus on the Circulation, *J. Clin. Investigation* **20** 127-144 (March) 1941.

10 Grollman, A. The Cardiac Output of Man in Health and Disease, Springfield, Ill., Charles C. Thomas, Publisher, 1932.

11 Liljestrand, G., and Stenstrom, N. Clinical Studies on the Work of the Heart During Rest. II. The Influence of Variation in the Hemoglobin Content in the Blood Flow, *Acta med. Scandinav.* **63** 130-141, 1925. Dautrebande, L. Le debit cardiaque dans l'anemie, *Compt. rend. Soc. de biol.* **93** 1029-1031 (Oct.) 1925. Pellegrini, G. Portata cardiaca e gittata pulsatoria negli anemici e modificazioni di esse dopo transfusione di sangue, *Boll. d. Soc. med-chir., Pavia* **48** 611 and 673, 1934.

patients tested twice, the circulation diminished as the hemoglobin increased, a fact suggesting that acceleration of the circulation was compensating for the hemoglobin deficiency. But when the results in table 3 are inspected it is evident that most anemic patients do not have hyperkinemia and that circulatory compensation must be a minor factor in most cases.

The miscellaneous subgroup consisted of 7 persons each suffering from a different disease. Since excitement may cause hyperkinemia in any one, these cases deserve no discussion.

TABLE 3—*Relation of Circulation to Hemoglobin Content in Anemia*

Date	Subject	Age, Yr	Hemo- globin Con- tent, Per centage	Red Blood Cells	Circulation per Minute per Pound of Body Weight, Percentage Deviation from Normal	Pulse Rate	Diagnosis
2/ 4/39	S O	18	64	3,700,000	+30	86	Purpura (capillary toxicosis)
10/30/39	C Z	35	63	3,600,000	-17	78	Biliary cirrhosis of liver
2/ 7/39	U S	69	61	2,700,000	-13	72	Arteriosclerosis, hypertension, cirrhosis of liver
1/ 1/36	F M	59	58	2,600,000	+28	98	Primary pernicious anemia
11/22/39	K F	18	53	2,500,000	-26	69	Aplastic anemia
11/28/41	R S	27	52	3,800,000	-13	72	Iron deficiency anemia
11/29/39	J M	55	50	2,600,000	+48	90	Secondary anemia, ? cause
12/21/39	A P	21	50	3,900,000	- 4	82	Subacute glomerulonephritis
2/28/40	A P		61	3,500,000	-22	92	Subacute glomerulonephritis
10/28/37	C K	59	48	2,800,000	+13	85	Duodenal ulcer, hemorrhage
9/18/39	E G	18	45	2,200,000	0	95	Chronic anemia (unclassified)
9/18/37	J Q	56	40	1,600,000	+17	101	Primary pernicious anemia
11/29/37	T R	59	38	2,600,000	- 9	68	Duodenal ulcer, hemorrhage
11/ 8/40	F H	50	37	2,700,000	+24	84	Bleeding hemorrhoids
1/ 2/37	O P	43	37	2,000,000	+55	84	Duodenal ulcer, hemorrhage
10/30/39	C K	37	35	1,700,000	+ 9	120	Duodenal ulcer, hemorrhage
5/13/38	H C	58	34	1,200,000	+ 9	70	Primary pernicious anemia
5/20/38	H C		57	2,300,000	-13	48	Primary pernicious anemia
1/31/40	E D	26	28	2,600,000	-22	84	Idiopathic hypochromic anemia
2/13/40	E D		67	3,600,000	-39	67	Idiopathic hypochromic anemia
1/12/38	M K	34	22	2,400,000	+22	100	Idiopathic microcytic anemia
1/29/38	M K		67	4,000,000	+ 4	62	Idiopathic microcytic anemia
12/18/39	E H	17	20	2,600,000	+ 4	94	Chlorosis
1/17/40	E H		67		-26	90	Chlorosis

b

The remaining subgroup, having the condition we have called essential hyperkinemia, is especially interesting, because this finding throws new light on hyperkinemia. We have studied 17 patients with essential hyperkinemia, chiefly young adults of both sexes.

Their symptoms were always mild. All denied weakness, although several admitted that they tired easily. Thirteen thought of themselves as nervous. Seven when questioned closely admitted dizziness on change of position, usually immediately after arising but often on bending over and sometimes when lying down. This was never a major complaint, and only 1 patient had ever fainted, and she only once. Five

thought they had undue dyspnea on exertion, in 6, palpitation was judged to be excessive. Two complained of attacks of indefinite precordial pain not related to exercise.

Examination disclosed that they were usually underweight, none was over his ideal weight, and the average was 14 pounds (6.4 Kg) under this figure. The pulse rate tended to be a little rapid, averaging 91. After a rest of fifteen minutes, the pulse rate was still over 100 in 5 subjects, but it was under 75 in 3. The thyroid was palpable in 5 patients. Excessive tremor of the extended hands was noted in 6.

The blood pressure was never elevated, averaging 124 systolic and 75 diastolic. The basal metabolic rate was always within normal limits, averaging — 2 per cent. In contrast, the circulation averaged 35 per cent over the expected normal. Routine blood counts and urinalyses revealed nothing abnormal, and electrocardiograms, secured in 10 cases, showed nothing of importance.

A number of brief case reports will serve to acquaint readers with the outstanding features of these cases (the records of several are shown in figure 1).

CASE 1—A. T., a man aged 33 years, was 5 feet 6 inches (167.6 cm) tall and weighed 121½ pounds (55.1 Kg). During the preceding twenty years he had had repeated admissions and operations for chronic osteomyelitis of the left femur and the right tibia, and the wounds had continued to drain a little. Nervousness was first noted one year before. Since then there had been palpitation on exertion and excitement and more dyspnea on exertion than formerly.

Physical examination disclosed slight exophthalmos, slight diffuse thyroid enlargement, slight tremor of the extended hands and draining scars at the right knee and in the left inguinal region. The pulse rate varied between 75 and 105. The patient was afebrile.

Every examiner agreed with the tentative diagnosis of hyperthyroidism, but basal metabolic rates determined in two laboratories were — 9, — 9, — 19 and — 6 per cent. The circulation was + 57 per cent and the pulse rate 96. An electrocardiogram was normal.

CASE 2—W. T., a man aged 50 years, an electrician, was 5 feet 8 inches (172.7 cm) tall and weighed 126 pounds (57.2 Kg). He complained of a tired feeling, a lack of appetite, constipation and dizziness on suddenly arising to his feet. He had lost 25 pounds (11.3 Kg) over a period of years.

Physical examination disclosed a relaxed abdominal wall and a low blood pressure, generally under 90 systolic and 65 diastolic. There was no tachycardia. The tentative diagnosis was hyperthyroidism, but the basal metabolic rate was — 10 per cent. The circulation was just above the upper normal limit, the pulse rate was 70.

An abdominal binder alleviated many of his symptoms.

CASE 3—C. A., a man aged 29 years, a janitor, was 5 feet 7 inches (170.2 cm) tall and weighed 137 pounds (62.1 Kg). For the past year he had complained of nervousness, burning of the eyes, headache, loss of energy and rapid heart action. His doctor had diagnosed thyrotoxicosis and sent him to the surgical service for thyroidectomy.

Physical examination showed a slightly enlarged soft thyroid. Two estimates of the basal metabolic rate gave results of + 7 and — 7 per cent. The circulation was + 30 per cent and the pulse rate 110.

CASE 4—J R, a man aged 32, a clerk, was 5 feet 7 inches (170.2 cm) tall and weighed 125 pounds (56.7 Kg). For the past year he had suffered from attacks of precordial distress accompanied by weakness, faintness, a sensation of epigastric fulness, belching and pain on the medial side of the left arm. These attacks occurred after eating, not after exercise. There was also epigastric "burning" relieved by food. Angina pectoris had been diagnosed by the attending physician, certainly on insufficient grounds.

Physical examination showed nothing abnormal. Gastrointestinal roentgen examination gave negative results. An electrocardiogram showed a slight abnormality attributed to the digitalis the patient had received before admission. The basal metabolic rate was  $-16$  per cent, the circulation was  $+30$  per cent and the pulse rate was 59.

CASE 5—A T, a man aged 42 years, a riveter, was 6 feet (182.9 cm) tall and weighed 170 pounds (77.1 Kg). Palpitations and a cardiac irregularity had worried him for the past two years, and his worry increased until he was unable to sleep. He also suffered from Raynaud's syndrome in his hands, probably secondary to his occupation.

Physical examination revealed a look of apprehension. The thyroid was diffusely enlarged. There were occasional ventricular extrasystoles. The basal metabolic rate was  $-17$  and  $-13$  per cent. The circulation was  $+26$  per cent and the pulse rate 90.

A psychiatric consultant unearthed a history of insecurity caused by a quarrel with his boss and believed the resulting anxiety was sufficient to account for the symptoms.

CASE 6—J D, a man aged 25 years, a hospital employee, was 5 feet 11 inches (180.3 cm) tall and weighed 148 pounds (67.1 Kg). For the past year he had suffered from spells of dizziness, which usually, but not always, occurred when he stood erect. Other complaints were nervousness and substernal pain not related to exercise. All these were mild, and it was acute diarrhea which first brought him to the dispensary.

Physical examination showed nothing abnormal except constant fidgeting. The basal metabolic rate was  $+14$  per cent. The circulation was  $+57$  per cent on the first test and  $+35$  per cent two months later, the pulse rate being 90 and 74, respectively.

CASE 7—S P, a woman aged 27, a housewife, was 5 feet 3 inches (160 cm) tall and weighed  $101\frac{1}{2}$  pounds (46 Kg). Tachycardia was always the outstanding feature of this case, it had been present for many years and was accompanied by few symptoms. Nevertheless, the thyroid having been palpable, a partial thyroidectomy had been performed three years before, without any improvement. When examined the patient insisted she was well and went to physicians only to allay the fears of her husband. She acknowledged that she tired easily. Palpitation was noted only after exercise.

Physical examination showed nothing abnormal except tachycardia, the rate being 104 after fifteen minutes of rest. The basal metabolic rate was  $-2$  per cent and the circulation  $+35$  per cent.

Evidently besides the hyperkinemia, the feature common to the great majority of the patients in this subgroup was a close resemblance of their symptoms to those of thyrotoxicosis in spite of a normal basal metabolic rate.

## COMMENT

Any study of clinical hyperkinemia is complicated by a factor not present when hypokinemia is investigated. Hyperkinemia may be readily induced in any subject by drugs such as epinephrine and amyl nitrite and then allies or by excitement. Emotion is so hard to produce experimentally that the accidental demonstration of a striking emotional effect deserves special mention.

CASE 8—E. T., a woman of 54 years, was known to have had hypertension for six years. She also had a uterine fibroid tumor which was large enough to encroach on the capacity of the bladder and lead to occasional incontinence.

In a routine study of the circulation in hypertension, the first of projected duplicate estimations by the ethyl iodide method had been completed uneventfully when incontinence supervened to the great annoyance and embarrassment of the patient. Nevertheless, she gamely continued to breathe through the apparatus while the operators, realizing that something had happened but ignorant of what it was, continued to take samples and make observations. Before the accident the results showed nothing abnormal except the blood pressure. After it, the emotional tension increased the cardiac output by 85 per cent, the pulse rate by 37 per cent, the volume of respiration by 89 per cent and the oxygen consumption by 77 per cent, while the blood pressure changed from 220 systolic and 120 diastolic to 260 systolic and 152 diastolic in millimeters of mercury.

Therefore hyperkinemia may indicate an emotional state as well as a primary physiologic condition. Only when it is found repeatedly in an individual patient or in a group of similar patients can it be taken as indicating the latter. The finding of it occasionally in association with any diseased condition is to be expected and deserves no emphasis.

The data in this paper, together with those published before,<sup>1</sup> permit certain generalizations which deserve discussion. It is evident that in many of the instances in which it is encountered in disease, hyperkinemia may serve a useful purpose. In hyperthyroidism and fever it meets the demands of increased tissue metabolism. In pulmonary disease and anemia it aids in overcoming a handicap which threatens to deprive the tissues of their normal supply of oxygen. In the case of abnormal intercirculatory communications it maintains the blood supply to the vital organs in spite of the tendency of the communication to draw blood from them. When found in advanced hypertensive cardiovascular disease it may represent a final attempt on the part of the body to maintain the blood supply of diseased organs, such as the kidneys. Only in essential hyperkinemia is one left without any clear idea of either the purpose or the causation of the abnormality. In this connection three questions present themselves.

The first question concerns the relationship of essential hyperkinemia to the neuroses. Are the subjects affected simply abnormally emotional persons who, confronted with the unusual situation inherent in making any test, react by the hyperkinemia of excitement? This

conception does not satisfactorily explain the findings. In the resident patients the pulse rates found at the time of our tests did not differ materially from those often found in the ward. Also, if excitement were the cause of the findings one would expect that the more arduous estimation of basal metabolic rate would produce enough emotion to increase that rate. Our patients had normal basal rates. So we do not think that emotion is the whole explanation of our findings, though we would be the last to deny that it might have influenced the results in some cases.

The second question concerns the relation of this type of hyperkinemia to the secretion of epinephrine or of sympathin. In some respects there are striking similarities between the clinical picture presented by our patients and that found in any normal subject after an injection of epinephrine. Hyperkinemia, tachycardia, tremor, apprehension, palpitation and sometimes dizziness irrespective of position are found in both. In several of our patients an injection of epinephrine chloride reproduced the subjective symptoms of which they commonly complained, Kessel and Hyman<sup>12</sup> made the same observation. But the differences are striking also. In essential hyperkinemia there is neither hypertension nor increased metabolic rate, which are regularly found after an injection of epinephrine chloride. To attribute essential hyperkinemia to an increased secretion of epinephrine would be unjustified in the light of present knowledge.

The third question is concerned with the relation of essential hyperkinemia to thyroid dysfunction. In spite of the normal basal metabolic rate found in all the patients with essential hyperkinemia, slight enlargement of the thyroid occurs far more frequently in such patients than in the general population. Certainly the superficial resemblance to patients with thyrotoxicosis is often striking. We have a point to add to the evidence for a relationship. In several of our cases of thyrotoxicosis, after partial thyroidectomy the metabolic rate has returned to normal before the circulation, leaving the patient temporarily in a condition indistinguishable from essential hyperkinemia (fig 3B). This observation amplifies the well known fact that after this operation the metabolic rate often returns to normal before the pulse rate. The idea of multiple thyroid hormones is old,<sup>13</sup> and if one stimulated the circulation without stimulating the metabolic rate it would explain our findings. Nevertheless, 1 of our patients with essential hyperkinemia underwent partial thyroidectomy, and 3 others had roentgen therapy to

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12 Kessel, L., and Hyman, H. T. Studies of Graves' Syndrome and the Involuntary Nervous System. II. The Clinical Manifestation of Disturbances of the Involuntary Nervous System (Autonomic Imbalance), *Am J M Sc* **165** 513-530 (April) 1923

13 Crotti, A. Thyroid and Thymus, Philadelphia, Lea & Febiger, 1922

the thyroid without any improvement. One patient has been followed for ten years, and thyrotoxicosis has not developed. Kessel and Hyman<sup>12</sup> have reported similar cases. If essential hyperkinemia should prove to be due to thyroid dysfunction, it is not the *forme fruste* of the older authors<sup>13</sup> but a different type from any now known.

Even if little conclusive can be said about causation, such patients will be familiar to every experienced clinician, for theirs are the cases in which the history, appearance and physical findings suggest hyperthyroidism although the basal metabolic rate is found to be normal. Cases which we believe to be similar have been studied in the army by Peabody, Wearn and Tompkins,<sup>14</sup> who called the condition "irritable heart" and in civil life by Kessel and Hyman,<sup>12</sup> who gave it the name of "autonomic imbalance." In 7 apparently similar cases, the trouble being called "prebasedow," the cardiac output was demonstrated to be above normal by Bansi,<sup>15</sup> and in 2 in which the diagnosis was "parabasedowism" or sympathicotonia, Lequime<sup>7d</sup> reported the same finding. All these terms imply more than is known, for the ultimate cause may be neither in the heart nor in the thyroid, and the trouble may be of humeral rather than of nervous origin. The term essential hyperkinemia is purely descriptive, admits ignorance of the fundamental causation and indicates the major physiologic abnormality.

The results suggest the reason why such cases are often confused with cases of hyperthyroidism. Hyperkinemia is common to both. A question immediately arises, Are not many of the manifestations of hyperthyroidism so often recognized at a glance by experienced clinicians due to the increased circulation rather than to anything more immediately associated with the metabolic rate? If this was true, patients with hyperthyroidism on showing cardiac complications would be expected to lose part of the characteristic manifestations. We are inclined to believe that this often happens, for we can think of a number of patients with cardiac complications whose hyperthyroidism went unrecognized for a long time because it occurred to no one to estimate the basal metabolic rate.

But we do not contend that all patients with hyperkinemia have an appearance which suggests the patient with hyperthyroidism. Some certainly have, and others have not, but additional factors present, such as anemia, pulmonary disease or other severe illnesses, may cause so

14 Peabody, W., Wearn, J. T., and Tompkins, E. H. Metabolism in Irritable Heart, *M. Clin. North America* 2: 507-515 (Sept.) 1918.

15 Bansi, H. W. Kreislaufstudien beim Basedow und bei der Herz-neurose, *Ztschr. f. klin. Med.* 110: 633-684, 1929.

many signs and symptoms themselves that those due to hyperkinemia may not be apparent

Figure 3 has been designed to show the relation between the circulation and the metabolic rate whenever one or both are abnormal, the data being derived from both this and previous papers<sup>16</sup>

In figure 3 *A* are given the results obtained in cases of hyperthyroidism without valid evidence of cardiac involvement and in cases of

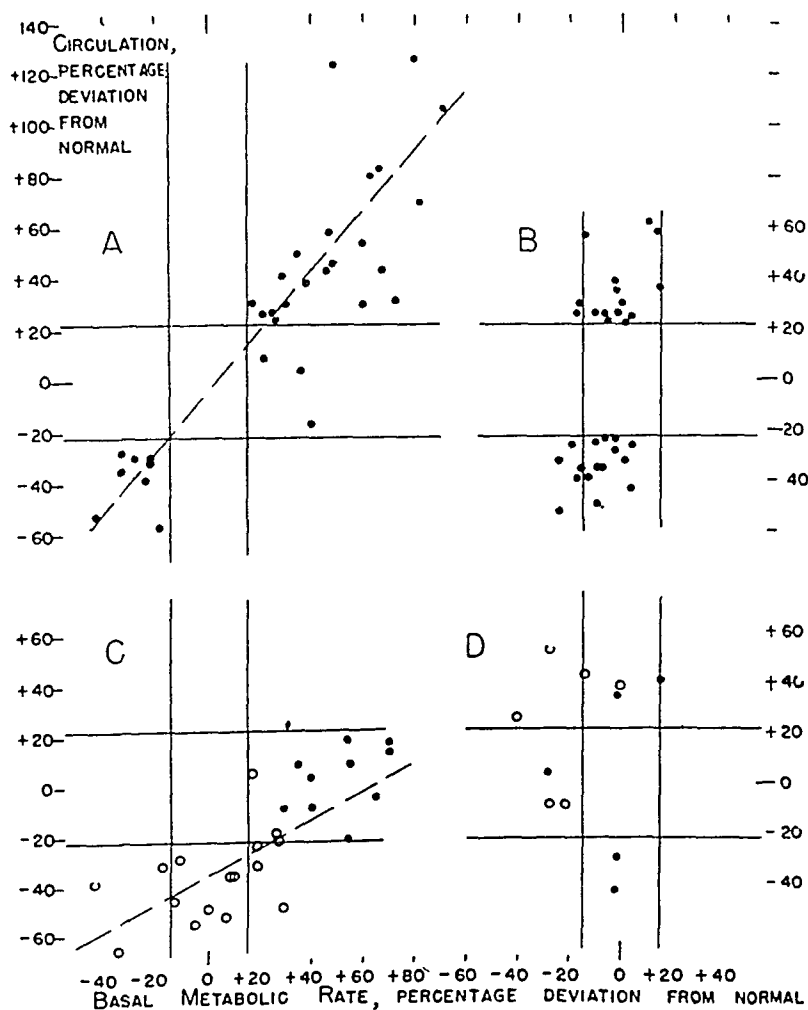


Fig 3—Graphs showing the relation between abnormalities of the circulation and the basal metabolic rate. The solid lines indicate the normal limits, so the enclosed rectangles define the area in which both circulation and metabolic rate were normal. *A*, data on patients with hyperthyroidism and hypothyroidism without known cardiac involvement. The broken line is the calculated line of best fit (regression,  $y$  on  $x$ ). *B*, data on patients with essential hyperkinemia and hypokinemia. *C*, the dots represent the results for patients with hyperthyroidism giving evidence of cardiac complications. The circles represent the results for patients with serious cardiac disease who had recovered from congestive heart failure. *D*, the dots represent the results obtained for patients who had had hyperthyroidism treated by partial thyroidectomy. The circles indicate the results obtained for certain emaciated persons.



hypothyroidism also. There is excellent correlation between the circulation and the metabolic rate in these cases, the coefficient is 0.84, any value over 0.28 being significant. Indeed, the line of best fit passes almost directly through the origin, and its slope is close to unity.

The relation of the circulation to the metabolic rate finds physiologic expression in the arteriovenous oxygen difference. This has been much studied in hyperthyroidism, some authors<sup>17</sup> finding a diminution on the average and others little change. Our results support the latter group but it should be noted that the variation of results in individual cases is large, so we are not surprised at the divergence of the averages obtained.

In 13 of our patients the basal metabolic rate was elevated but the circulation was within normal limits. There is collateral evidence that all but 3 of these patients suffered from cardiac involvement. Four had definitely enlarged hearts as estimated by orthodiagram, in 4 others edema of the ankles was demonstrated on admission. Another suffered from attacks of auricular fibrillation. In still another the liver was 4 cm. below the costal margin at the time the circulation was within normal limits, after several days of rest in bed the liver diminished in size and the circulation was then found to be above normal. Of the remaining 3 patients, 1 suffered from multiple bony metastases from a carcinoma of the breast in addition to the thyrotoxicosis. The 2 remaining patients showed no positive collateral evidence of cardiac involvement, but 1 was extremely prostrated by her disease. Another patient with hyperthyroidism, severe cardiac insufficiency and normal circulation has been reported on by Lequime.<sup>7d</sup>

In figure 3 C are shown data on our 10 patients with thyrotoxicosis with evidence of cardiac involvement and also on a group of patients who had either recovered from congestive heart failure or shown evidence of severe cardiac disease.<sup>6b</sup> None were in failure when the test was made. It will be seen at once that there was a significant correlation between the circulation and the metabolic rate of all these patients, the coefficient being 0.69, whereas any value above 0.32 is significant. But one should note that these patients had smaller circulations in proportion to their metabolic rates than the patients without cardiac complications, whose data are shown in figure 3 A. In figure 3 C the line of best fit passes far below the origin and the slope is only about 0.5.

These statistics lead to the following conclusions. In the absence of cardiac disease abnormal increments or decrements of basal metabolic rate are accompanied, on the average, by corresponding percentage

17 Bansi, H. W., and Groscurth, G. Die Kreislauleistung beim Basedow und Myxodem, *Ztschr. f. klin. Med.* **116** 583-602, 1931. Goldbloom, A. Clinical Studies of Circulatory Adjustments, *Clinical Evaluation of Cardiac Output Studies*, *Internat. Clin.* **3** 206-245 (Sept.) 1936. Footnote 7.

changes in the circulation. In the presence of cardiac disease the circulation is smaller than one would expect from the metabolic rate, and the deficit increases with each increment of metabolic rate. Therefore an increased metabolic rate without a corresponding increase in the circulation suggests cardiac disease. Also, the data provide a reason for the success of the old clinical practice of reducing the metabolic rate in cases of heart disease by such measures as rest, diet and use of sedatives, for when this rate is at a minimum the circulatory deficit is also at a minimum. A somewhat similar viewpoint provided the theoretic basis for Blumgart's<sup>18</sup> trials of thyroidectomy in cases of cardiac disease.

In figure 3 *B* have been placed the data obtained for the subgroups with what we have called essential hyperkinemia and hypokinemia. The former patients have been discussed in this and the latter in a previous publication.<sup>1</sup> A comparison of figure 3 *B* with figure 3 *C* discloses that the circulation and the metabolic rate in patients with essential hypokinemia are identical with those of patients suffering from organic heart disease. The two groups doubtless share the symptoms dependent on their common abnormality, and it is not surprising that when the relation was not understood such a term as functional heart disease was employed. It is a poor term because the hearts of patients with essential hypokinemia are normal by any test now known, and the trouble should be sought elsewhere in the circulation.

In figure 3 *D* are given data obtained for other conditions in which the relation between circulation and metabolism was abnormal. An abnormal relation has been found frequently in emaciation, the results suggesting that the basal metabolic rate may diminish, as it regularly does in starvation,<sup>19</sup> but the circulation may not accompany it downward. We have occasionally found this abnormality after partial thyroidectomy, the circulation being above normal in some cases and below it in others, as if the operation had interfered with the normal coordination of circulation and metabolism.

#### SUMMARY

In a total experience of about 1,400 estimations of cardiac output, 100 patients were encountered in whom the resting circulation was above

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18 Blumgart, H. L., Levine, S. A., and Berlin, D. D. An Attempt to Reduce the Basal Metabolic Rate of Cardiacs by Subtotal Thyroidectomy, *Arch. Int. Med.* **51** 867-877 (June) 1933. Blumgart, H. L., Riseman, J. E. F., Davis, D., and Berlin, D. D. Therapeutic Effect of Total Ablation of Normal Thyroid on Congestive Heart Failure and Angina Pectoris. Early Results in Various Types of Cardiovascular Disease and Coincident Pathologic States Without Clinical or Pathologic Evidence of Thyroid Toxicity, *ibid.* **52** 165-225 (Aug.) 1933.

19 Du Bois, E. F. Basal Metabolism in Health and Disease, Philadelphia, Lea & Febiger, 1936.

normal, a condition we have called hyperkinemia. These patients were usually underweight, and they tended to have resting pulse rates above normal.

Hyperkinemia was encountered in almost all patients with thyrotoxicosis without cardiac involvement and in most patients with patent ductus arteriosus. It was found often in patients with emaciation and less frequently in those with pulmonary abnormalities, fever, anemia, hypertension and peripheral arteriovenous communications.

In 17 patients, hyperkinemia was present without any complicating condition having been discovered. These patients with essential hyperkinemia resembled patients with thyrotoxicosis in appearance, but the basal metabolic rate was always normal. The clinical characteristics of this subgroup have been described in detail.

The relation between abnormalities of the circulation and the basal metabolic rate has been studied by statistical methods. In uncomplicated hyperthyroidism and hypothyroidism the relation is almost 1 to 1, i. e., on the average, an abnormal increment or decrement in the basal metabolic rate is accompanied by an equal percentage change in the circulation. In heart disease these two functions are related, but the relationship is more nearly 1 to 0.5. Under such conditions the circulation is less than normal for any given metabolic rate, and the higher the metabolic rate the greater is the circulatory deficit.

Other instances of deviation from the normal 1 to 1 relationship between circulation and metabolic rate have been found in cases of emaciation and in some cases of hyperthyroidism after partial thyroidectomy.

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# CHRONIC GASTRITIS SIMULATING GASTRIC CARCINOMA

REPORT OF FIVE CASES

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As a result of refinements in technic of roentgen examination of the stomach and the introduction of the flexible gastroscope, chronic gastritis has received renewed attention. Chronic gastritis is frequently a generalized involvement of the stomach, but often it can be of severe degree and localized in various parts of the stomach. While the roentgen appearance of generalized hypertrophic gastritis can often be recognized, the localized forms are frequently difficult to differentiate from carcinoma. Even gastroscopically the differentiation between a localized inflammatory infiltration and one which is neoplastic cannot always be made.

Brunn and Pearl<sup>1</sup> first called attention to the fact that a malignant lesion can be simulated by chronic hypertrophic gastritis. Subsequently, Konjetzny<sup>2</sup> and Schindler<sup>3</sup> reported similar instances. In the past three years we have encountered 5 cases in which the roentgen and gastroscopic appearance of localized chronic hypertrophic gastritis simulated carcinoma of the stomach.

The difficulties in diagnosis presented by these cases were such that carcinoma could not be excluded before an exploratory laparotomy was done. In 3 of the cases the true nature of the lesion did not become apparent until histologic examination of the resected specimens was made.

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From The University Hospitals and the Institute of Pathology, Western Reserve University

1 Brunn, H, and Pearl, F. Diffuse Gastric Polyposis, Adenopapillomatosis Gastrica, Surg, Gynec & Obst **43** 559 (Nov) 1926

2 Konjetzny, G E. Der Magenkrebs, Stuttgart, Ferdinand Enke, 1938, reviewed, J A M A **112** 1631 (April 22) 1939

3 Schindler, R. Gastritis Simulating Tumor Formation, Am J Digest Dis **6**:523 (Oct) 1939

## REPORT OF CASES

CASE 1—A 30 year old white male chemist complained of persistent epigastric pain of three weeks' duration. The pain had no relation to food or eating. He had no other complaints except that he had lost 20 pounds (9 Kg) in weight. On physical examination he was undernourished and anemic, but otherwise normal. Laboratory examination of the blood yielded the following data: red cell count, 4,730,000, hemoglobin concentration, 45 per cent, and white cell count, 7,900. Gastric analysis showed a peak acidity of 8 units of free acid and 31 units of total acid. On examination the stool was strongly positive for occult blood. Clinically a lesion of the stomach was suspected and was thought to be a bleeding ulcer.

Roentgen examination (fig 1 *a*) showed an irregular deformity of the distal end of the body of the stomach on the side of the greater curvature. The involved area measured about 8 cm in length and 3.5 cm in width. The rugae throughout



Fig 1—(a) A roentgenogram showing irregular contour and polypoid defects in the lumen on the side of the greater curvature of the body of the stomach. Note the normal rugae on the side of the lesser curvature. (b) A photomicrograph ( $\times 130$ ) showing lymphocytic infiltration of the gastric mucosa.

this area were markedly enlarged and distorted by several circular polypoid defects but were normal elsewhere. Peristalsis was absent in the involved portion. A diagnosis of carcinoma of the body of the stomach on the side of the greater curvature was made.

Gastroscopic examination revealed a normal antrum except for pallor of the mucous membrane. On the anterior wall 3 to 4 cm above the antrum there was a distinct change in the appearance of the mucosa. There was a prominent, irregular, pale pinkish gray, nodular semicircular fold, which looked like the raised margin of a malignant ulcer. Proximal to this fold only small islands of irregular pale pink and hyperemic mucosa were visible in an otherwise homogeneous

surface covered with gelatinous greenish gray material. There was a suggestion of rugae extending through this region. These were thickened and irregular with multiple superficial hemorrhagic erosions. The lesion extended up to the fundus on the anterior wall and the greater curvature, but on the lesser curvature and the posterior aspect the mucosa showed only pallor and some irregularity of rugae. An infiltrative lesion involved the upper two thirds of the anterior wall and the greater curvature of the corpus of the stomach. The localization suggested that it was neoplastic, but the possibility of its being inflammatory could not be excluded.

At operation the stomach was found to be slightly dilated, the proximal half being paler than the distal portion. The wall of the corpus was distinctly lobulated and had a definite yellow color in contrast to the pink distal portion. On the surface of the body of the stomach there were numerous large dilated intercommunicating veins, which gave the serosa a mosaic pattern. Palpation revealed this portion of the stomach to be thicker than the rest. Exploration of the interior of the stomach revealed extensive redundancy and thickening of the mucosa and the submucosa.

Biopsy included a portion of the mucosa and the submucosa. Microscopic examination revealed a definite increase in the number of lymphocytes and plasma cells and also scattered polymorphonuclear neutrophilic leukocytes throughout the mucosal connective tissue (fig 1 *b*). A regional lymph node was also removed which showed moderate diffuse hyperplasia of the reticular cells. These changes were indicative of acute and chronic gastritis and endothelial hyperplasia of the regional lymph node.

CASE 2—A 29 year old white man had for two years often vomited at night, the vomitus frequently containing clots of bright red blood. On an ulcer regimen the vomiting decreased. For six months he had dull, gnawing epigastric pain two to three hours after meals and at night, which was frequently relieved by taking alkali and milk. He had lost 20 pounds in weight. On physical examination he showed pallor and evidence of undernourishment. There was tenderness to palpation around the umbilicus and in the epigastrium. Laboratory examinations of the blood revealed a red cell count of 4,420,000, a hemoglobin concentration of 56 per cent and a white cell count of 8,000. Gastric analysis after stimulation with histamine failed to reveal any free acid. The total acid was 12 units. On examination the stools gave a strongly positive reaction for occult blood. Clinically, an ulcer with bleeding was suspected, though the anacidity was a disturbing factor.

Roentgen examination (fig 2 *a*) revealed irregular defects of the contour in the cardiac portion of the stomach. These were most marked in the fundus, on the side of the greater curvature, there being only slight irregularity of the lesser curvature. In this region the rugae were distinctly widened. The pyloric portion was smooth in contour, and the rugae were of approximately normal width. The appearance suggested an infiltrating type of malignant tumor.

Gastroscopic examination was unsatisfactory. No contraction waves were noted in the antrum. In this region the mucosa had a distinctly granular surface with many pale pink, red and boggy gray areas. In many regions small amounts of adherent secretion and bright red blood were noted on the mucosal surface. Several

small hemorrhagic erosions were also noted. The corpus could not be seen because a considerable amount of blood-tinged fluid obscured vision.

At operation the stomach was found to be large. There were no palpable lymph nodes. On opening the stomach it was seen that throughout its proximal three fourths the mucosa was hyperemic, edematous and spongy. This abnormal mucosa ended abruptly in the prepyloric region where there were normal-looking gastric rugae. Gently wiping the abnormal mucosal surface readily produced bleeding.

Biopsy included mucosa and submucosa. The gastric glands were normal in number, elongated and tortuous, and some were distinctly dilated. Throughout the tunica propria there was an increase in the number of lymphoid and plasma cells, along with slight diffuse infiltration of polymorphonuclear leukocytes. The submucosa showed slight edema but no cellular infiltration (fig 2 *b* and *c*). A diagnosis of acute and chronic gastritis was made.

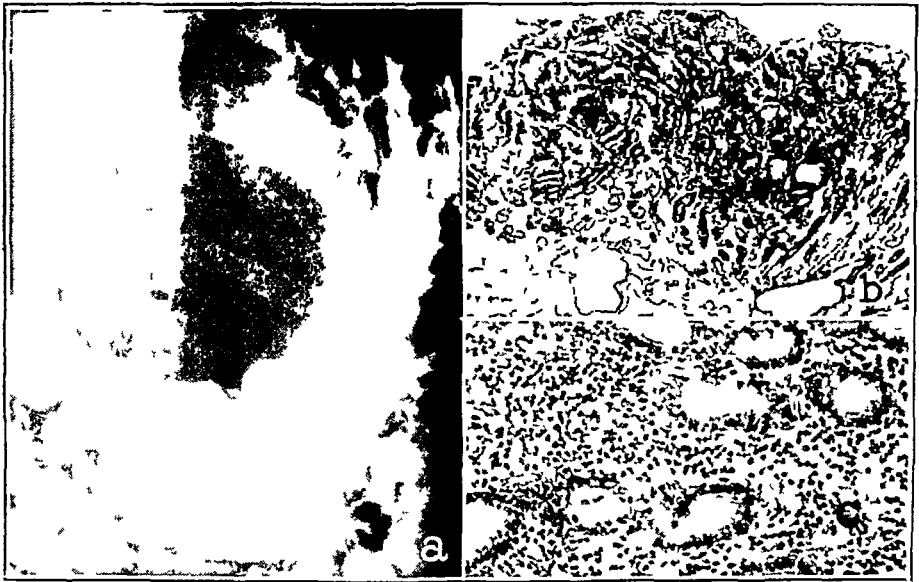


Fig 2—(a) A roentgenogram indicating the marked widening rugae in the cardiac portion of the stomach, irregularities of contour mainly on the side of the greater curvature and normal rugae in the pyloric portion. (b) A photomicrograph ( $\times 45$ ) illustrating elongation, tortuosity and dilatation of the gastric glands. (c) A photomicrograph ( $\times 86$ ) showing lymphocytic infiltration of the gastric mucosa.

CASE 3—A 50 year old white man complained of burning epigastric pain radiating under the sternum and anorexia of three months' duration. Food aggravated the pain, sodium bicarbonate relieved it. He had occasional vomiting and had lost 30 pounds (14 Kg) in weight. On physical examination he was undernourished and had signs of mitral stenosis and insufficiency. The abdomen was normal. Laboratory examination of the blood revealed a red cell count of 4,190,000, a hemoglobin concentration of 90 per cent and a white cell count of 7,500. Gastric analysis showed peak acidity of 20 units of free acid and 33 units of total acid. On examination the stools did not show any occult blood. Clinical opinion was about equally divided between gastric ulcer and carcinoma.

Roentgen examination (fig 3) revealed irregular contours of the cardiac end and the upper half of the body of the stomach, with various-sized oval and circular

defects within the lumen. The distal half of the stomach was normal. On account of our experience in several previous cases we thought that the changes were due to polypoid gastritis, although the possibility of polypoid carcinoma could not be excluded.

Gastroscopic examination showed the antrum and the pyloric canal to be normal and to function actively. A few centimeters proximal to the incisura on the anterior wall and the greater curvature there was much adherent greenish gray mucopurulent secretion. The mucosal surface was distinctly irregular because of many projecting rounded masses which appeared to be on the tops of large irregular nodular rugae. These protruding islands of mucosa showed many irregular areas of marked hyperemia, many petechiae and several small superficial erosions. On the lesser curvature and the posterior wall, the rugae appeared large and irregular and the mucosa had a mottled yellowish and greenish gray, roughly granular surface on which there were a few small hyperemic areas. In view of similar findings in a previous case the impression was that this was localized chronic hypertrophic gastritis.

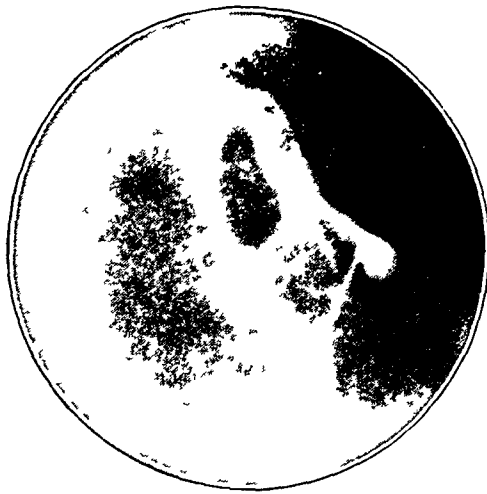


Fig. 3—A spot roentgenogram of the cardiac end of the stomach, showing oval and circular defects within the lumen and irregularities of contour.

At operation the stomach was palpated and visualized up to the esophageal hiatus. It had a normal external appearance, and there were no palpable masses and there was no induration. There were no palpable lymph nodes in the gastro-hepatic omentum and no peritoneal implants. The abdominal wall was closed without opening the stomach.

**CASE 4**—A 59 year old white woman had suffered attacks of indigestion for twenty years. These consisted of gnawing discomfort in the upper portion of the abdomen one hour after meals which was relieved by taking sodium bicarbonate dissolved in hot water. For five months she had had marked anorexia and fulness after little intake and had occasionally vomited. She had lost 30 pounds in two years. On physical examination she was emaciated and there was fulness in the left upper quadrant of the abdomen. Laboratory examination of the blood revealed a red cell count of 4,280,000, a hemoglobin concentration of 64 per cent and a white cell count of 8,100. Gastric analysis revealed a lack of free acid and 40 units of total acid after stimulation with histamine. On examination the stools were positive for occult blood. Clinically, a chronic peptic ulcer with pyloric obstruction and gastric carcinoma were considered.



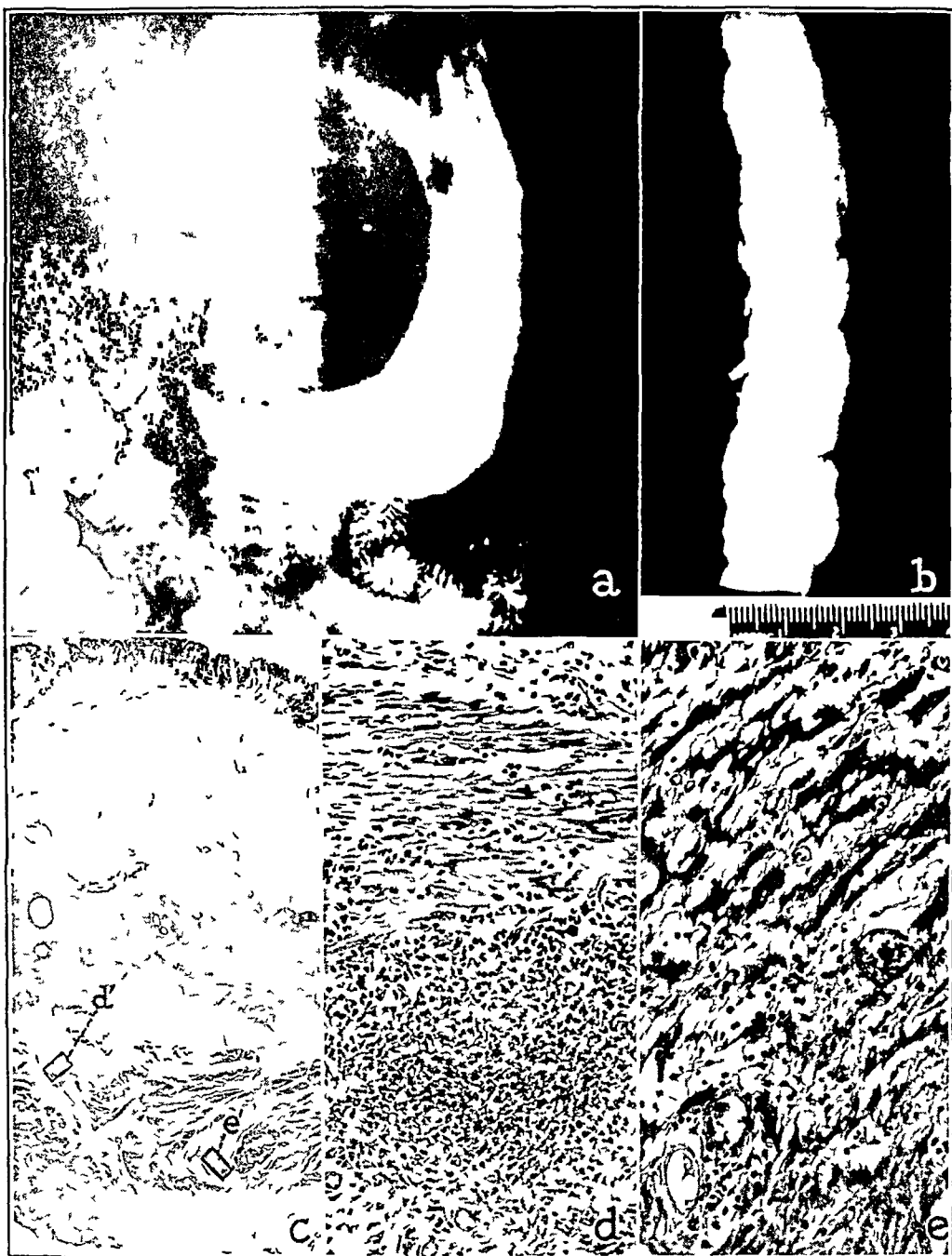


Fig 4—(a) A roentgenogram of the funnel-shaped narrowing of the pyloric end of the stomach, with absence of peristaltic waves. The rugae in the cardiac portion of the stomach are normal. (b) A photograph showing the increased thickness and edema of the wall of the stomach. (c) A photomicrograph ( $\times 57$ ) demonstrating the increased thickness of the submucosa and the separation of muscle fibers due to edema. The locations of *d* and *e* are indicated at *d'* and *e'*. (d) A photomicrograph ( $\times 145$ ) showing infiltration of the muscularis with lymphocytes, large mononuclear cells and polymorphonuclear leukocytes. (e) A photomicrograph ( $\times 145$ ) illustrating edema and lymphocytic infiltration of the muscularis.

Roentgen studies (fig 4*a*) showed the stomach to be elongated and atonic and to contain more fluid than usual. The pyloric end was rigid, funnel shaped and markedly narrowed. In this region peristaltic waves were absent. The corpus and the fundus were normal. There was 30 per cent retention at the end of six hours. On reexamination several days later, after medication with atropine, these findings were unchanged. A diagnosis of infiltrating lesion of the pyloric end of the stomach, probably an annular carcinoma, was made.

At operation the pyloric end of the stomach was found to be markedly thickened, hard and irregular in contour over an area measuring about 8 cm in diameter. There was no peritoneal involvement. A few small gastric lymph nodes were noted on the side of the lesser curvature. The appearance of the lesion was that of a malignant tumor, and a subtotal gastrectomy was done.

The portion of the stomach removed showed marked changes. The mucosa was dull pale yellow, soft and edematous. The stomach sectioned with increased resistance and had an unusually thick wall, averaging 16 mm (fig 4*b*). The submucosa was greatly thickened, pale, glistening and firm. The other coats were moderately thickened and edematous. Microscopically there were diffuse lymphocytic infiltration and edema of all coats. The gastric glands were elongated and tortuous. The submucosa was unusually thick, principally because of edema. There was also edema of the muscularis, with actual separation of the muscle fibers. In all coats there were also focal collections of polymorphonuclear leukocytes, plasma and large mononuclear cells (fig 4*c, d, e*). A diagnosis of subacute and chronic gastritis was made.

CASE 5—A 64 year old white woman had had slight indigestion for two years. For five months she had had fairly severe pain in the upper portion of the abdomen, occurring four to five hours after meals, which was relieved by taking food and sodium bicarbonate. She had had persistent abdominal fullness and occasional vomiting. She had not lost any weight. Physical examination revealed nothing abnormal. Laboratory examination of the blood revealed a red cell count of 5,030,000, a hemoglobin concentration of 71 per cent and a white cell count of 10,200. Gastric analysis showed 39 units of free acid and 50 units of total acid. Clinically, carcinoma of the stomach was suspected.

Roentgen examination (fig 5*a*) revealed a constricting lesion of irregular contour throughout the prepyloric portion of the stomach. The findings were indicative of carcinoma.

Laparotomy revealed a tumor mass in the pyloric region, which was resected.

The wall of the resected portion of the stomach was increased in thickness (averaging 8 mm) and sectioned with increased resistance. The submucosa was particularly thickened and edematous.

Microscopically there was marked chronic inflammation with diffuse lymphocytic infiltration of all coats. The marked increase in the thickness of the submucosa was due in part to edema and in part to fibrosis (fig 5*b, c, d*). In this specimen there was a lesion measuring 7 mm in diameter which was not identified on gross examination. Microscopically it showed a small area where the mucosa was interrupted. The architectural pattern of the glands was abnormal, and there were unusually large glands, which were lined with atypical epithelium. In some portions the glands were also atypical in shape, and there were groups of epithelial cells without a glandular pattern. These cells were large, variable in size and had bizarre hyperchromatic nuclei. There were no abnormal mitotic figures and no

histologic evidence of invasion of the submucosa. Such lesions have been called carcinoma *in situ*<sup>4</sup> or carcinoma of noninvasive type (fig 6 *a, b, c*)

Another finding was the presence of many large atypical cells in the submucosa and the muscularis. These cells were large and varied in size and shape. Many were multipolar and spindle shaped, so that they appeared to be connective tissue cells. They had deeply chromatic nuclei and abundant pinkish blue cytoplasm.

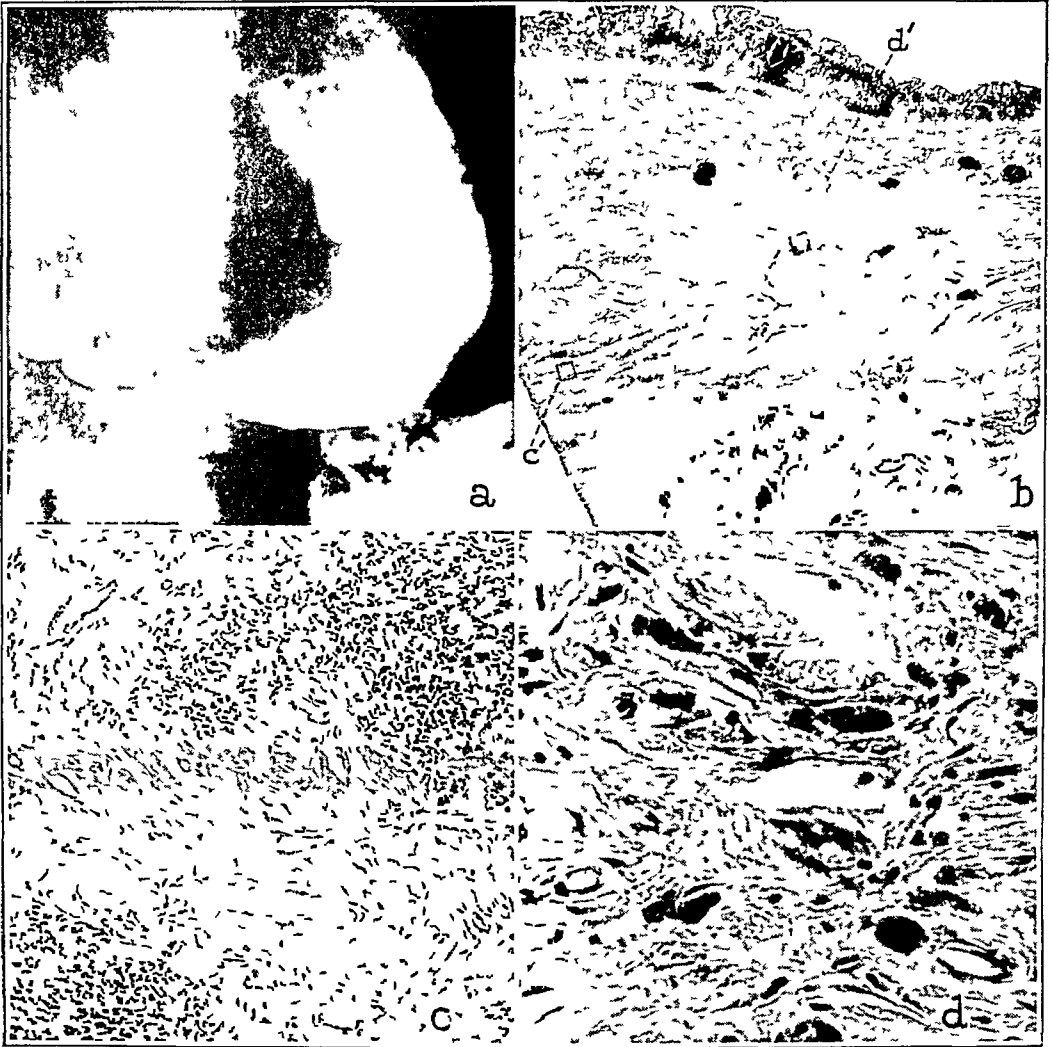


Fig 5—(a) A roentgenogram demonstrating an irregularly defined constricting lesion in the prepyloric portion of the stomach. (b) A photomicrograph ( $\times 6$ ) illustrating lymphocytic infiltration and increased thickness of the wall of the stomach. The locations of *c* and *d* are indicated at *c'* and *d'*. (c) A photomicrograph ( $\times 136$ ) showing marked lymphocytic infiltration of the muscularis. (d) A photomicrograph ( $\times 332$ ) demonstrating atypical mesenchymal cells in the submucosa.

An occasional cell contained two to four nuclei, but there were no abnormal mitotic figures. Sections stained with mucicarmine showed many of the cells to contain

4 Mallory, T. B. Carcinoma in Situ of the Stomach and Its Bearing on the Histogenesis of Malignant Ulcers, Arch Path 30:348 (July) 1940.

material that is usually identified as mucin. It is yet to be shown that such a substance is found in or formed by connective tissue cells. It is, therefore, impossible to state that these are not epithelial cells. They have tentatively been considered to be of mesenchymal type. A diagnosis of chronic gastritis and carcinoma *in situ* was made.

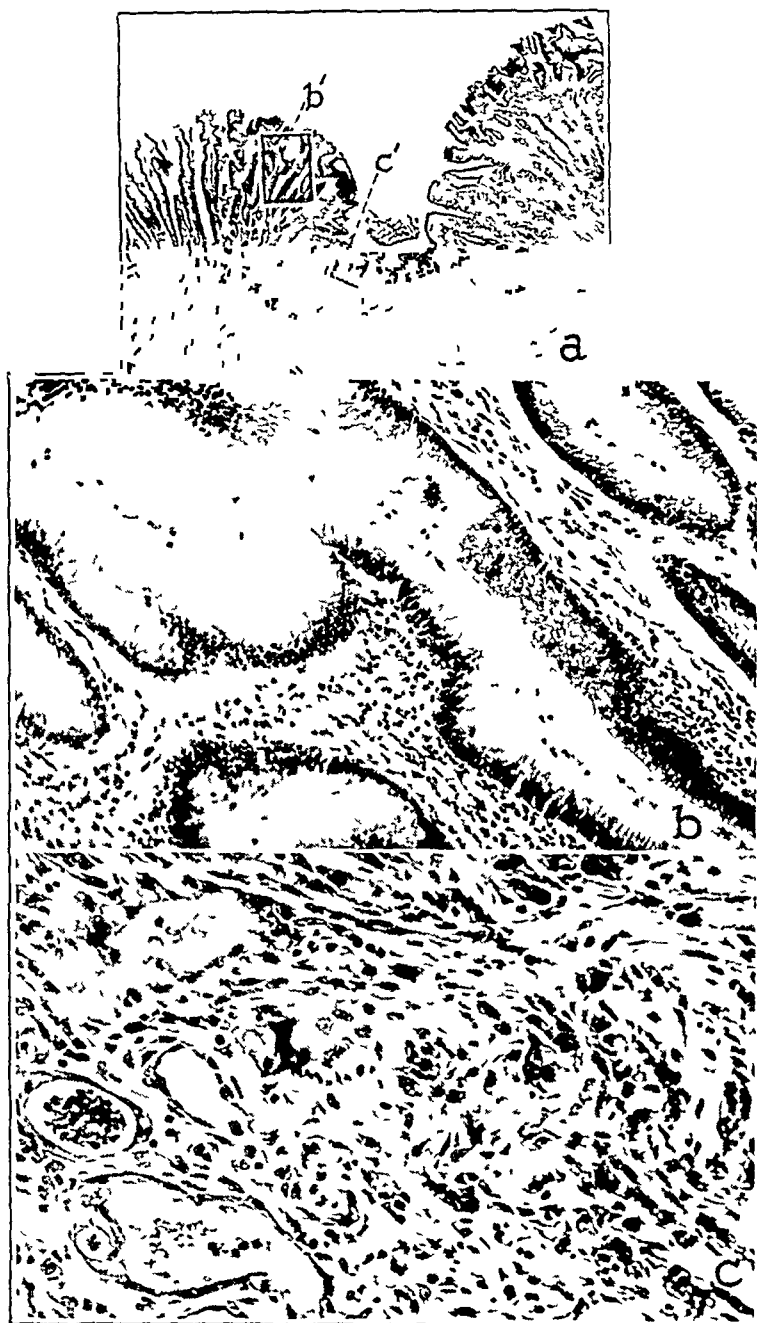


Fig 6 (a) A photomicrograph ( $\times 8$ ) illustrating atypical glands and focal atrophy of the gastric mucosa. The locations of *b* and *c* are indicated at *b'* and *c'*. (b) A photomicrograph ( $\times 138$ ) showing giant glands lined with high columnar mucin-secreting epithelium. (c) A photomicrograph ( $\times 178$ ) illustrating atypical glands and epithelial cells without a glandular pattern in the gastric mucosa.

This patient is at present, nearly three and one half years after operation, living, well and completely relieved of gastrointestinal symptoms.

## COMMENT

From the clinician's standpoint these cases call attention to the difficulties in making a definite diagnosis to guide the management of the patients. Inasmuch as treatment of gastritis is primarily medical unless it produces pyloric obstruction, the importance of utilizing all possible means to establish a diagnosis is obvious.

It is generally admitted that the symptoms of gastritis do not follow any characteristic pattern. In keeping with this opinion the patients in these cases did not have any characteristic complaint except epigastric pain. This, however, varied considerably in degree, duration, radiation, time of occurrence and method of relief. In 4 of the 5 cases the symptoms were associated with considerable loss of weight. The only significant abnormalities noted on physical examination were evidence of loss of weight and anemia. These facts served to enhance the clinical impression of carcinoma.

In regard to laboratory data the gastric analyses did not yield uniform results. Examinations of stools revealed the presence of occult blood in 3 of the 4 cases in which such examination was done. The most uniform finding was a hypochromic anemia, which was fairly severe in some of the cases and undoubtedly resulted from loss of blood. It has been our observation in these and in other cases that the more severe gastritides usually show marked hemorrhagic manifestations on gastroscopic examination. The loss of blood is usually gradual over a long period. It is thus understandable that none of these patients gave any history of melena, although in 1 case occasional vomiting of blood was noted. Attention has, however, been directed in the literature to the fact that gastritis can produce gross and sometimes even fatal hemorrhage. Nevertheless, loss of blood cannot be interpreted as characteristic of chronic gastritis, because carcinoma can produce exactly the same picture.

From the gastroscopic standpoint in the cases in which such examination was done the diagnosis was not definitely made because of the localized, though severe, nature of a lesion which is usually more diffuse and because the adherent secretion masked the true nature of the underlying condition. Since these cases were encountered, the more frequent use of lavage of the stomach preparatory to gastroscopic examination has proved helpful in arriving at a more definite impression in cases in which the diagnosis is questionable.

From the roentgenologist's standpoint the cases reported emphasize the importance of the extreme care necessary before making a diagnosis of carcinoma of the stomach. According to Berg,<sup>5</sup> gastritis is differ-

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5 Berg, H. H. Röntgenuntersuchungen am Innenrelief des Verdauungskanal, Ein Beitrag zur klinischen Röntgendiagnostik insbesondere von Entzündung, Geschwür und Krebs, Leipzig, Georg Thieme, 1930.

entiated from carcinoma either by generalized distribution of widened rugae rearranged in a mosaic-like pattern throughout the entire stomach or by its less frequent localization in the pyloric end. In cases of polypoid gastritis the defects produced may be circular in shape. He also states that chronic gastritis produces intraluminary defects, with occasional roughening and a "toothed contour" of the side of the greater curvature but without marked changes in the contour of the whole stomach. According to Berg, peristaltic waves usually traverse the involved area without interference.

From the reported cases, however, it is apparent that chronic gastritis if localized is not necessarily limited to the pyloric portion of the stomach. Case 1 demonstrates that it may be situated on the side of the greater curvature or, as in cases 3 and 4, it may involve only the cardiac portion of the stomach. Furthermore, chronic gastritis may eventually lead to a rigidity of the wall, with absence of peristaltic waves and to marked deformities of the contour (cases 1, 4 and 5). Occasionally it causes pyloric obstruction (case 4).

If the wide and irregularly arranged linear or polypoid rugae are associated with defects of contour, the differentiation between gastritis and carcinoma may be extremely difficult, indeed impossible. In such instances repeated examinations at short intervals may show some regression in the changes, favoring gastritis. In order to avoid diagnostic errors the roentgenologist must be conscious of these pitfalls and in certain instances should report the possibility of this less serious disease.

The pathologist often sees changes in the gastric mucosa which are slight. In many such instances it may be difficult to decide whether gastritis exists. This difficulty is probably in part due to the fact that the histologic appearance of the normal stomach of the adult is not too well known. It certainly seems possible that a normal adult's stomach is subjected to irritation by ingested coarse, hot and cold food, alcoholic drinks and other irritating substances. It has been shown<sup>6</sup> that although alcohol may produce hyperemia of and petechiae in the gastric mucosa, it does not cause any true inflammation. Berry<sup>7</sup> has pointed out that there is no evidence that significant gastritis results from the ingestion of alcohol provided there is an adequate intake of the vitamin B complex. It seems probable, therefore, that minor changes in the gastric mucosa may result from the ingestion of irritating substances,

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6 Hirsch, E. F. The Gastric Mucosa and Delirium Tremens, *Arch. Int. Med.* **17**: 354 (March) 1916.

7 Berry, L. H. Chronic Alcoholic Gastritis: Evaluation of the Concept, with Gastroscopic Studies in One Hundred Cases, *J. A. M. A.* **117**: 2233 (Dec. 27) 1941.

but that there is any significant inflammation is questionable. Because such minor changes in the stomach have been interpreted as chronic gastritis, the accuracy of such a diagnosis has frequently been questioned. Changes, however, in the stomach are sometimes encountered which are proof of a disease of unknown causation which is progressive and serious. In such instances the anatomic evidence of inflammation is indisputable. The conditions in all of the cases reported in this paper are of this type and should be considered as chronic nonspecific gastritis.

Chronic gastritis may affect principally the mucosa and the submucosa, or it may involve the entire thickness of the stomach. The types which principally involve the mucosa are usually called either chronic atrophic or chronic hypertrophic gastritis. In none of the cases described was the inflammation limited to the mucosa, in every one there was involvement of all coats of the stomach. The mucosa was in all instances involved and increased rather than decreased in thickness. In most of them varying degrees of acute and subacute inflammation were superimposed on the more marked chronic process. These, therefore, are all cases of chronic interstitial gastritis with hypertrophic mucosa.

The following principal changes were noted:

On gross examination, the stomachs were increased in size and consistency, had unusually thick walls and sectioned with increased resistance. In all, the mucosa was thick, dull and edematous, the submucosa was thick, edematous and in some instances gelatinous, and the muscularis was thick, somewhat edematous and unusually firm. By gross examination alone it was difficult to exclude diffusely infiltrative lesions like those of scirrhus carcinoma, lymphoblastoma and syphilis.

Microscopic examination showed cellular infiltration with lymphocytes, polymorphonuclear leukocytes and plasma cells, of all coats, most marked in the mucosa and the submucosa. There were also edema and fibrosis of all portions, particularly of the submucosa and the muscularis. The gastric glands were somewhat elongated and dilated. In some instances there was metaplasia of the glandular epithelium to the mucin-secreting type.

In case 5, in addition to the gastritis, there was carcinoma limited to the mucosa. Noninvasive epithelial tumors in the uterus<sup>8</sup> and in the stomach<sup>4</sup> are reported in the literature and have been called

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<sup>8</sup> Schiller, W. Untersuchungen zur Entstehung der Geschwulste. I. Teil. Collumcarcinom des Uterus, *Virchows Arch f. path. Anat.* **263**: 279, 1927. Younger, P. A. Preinvasive Carcinoma of the Cervix, *Arch. Path.* **27**: 804 (April) 1939.

“carcinoma *in situ*” The lesion in this case is that of carcinoma *in situ* with local invasion of the gastric mucosa. Some of the histologic features of this lesion are shown in the photomicrographs. The lesion measures 8 mm in its greatest diameter, and the mucosa is decreased in thickness in one portion (fig 6 *a*). In general, there is no striking alteration in the glandular pattern, but there are distinct changes in the size of the glands and in the character of the cells which line them. Some of the glands are unusually large (fig 6 *b*), and their lining cells have hyperchromatic nuclei and in some instances loss of nuclear polarity. In some regions the glands are atypical in shape, and there are many epithelial cells in the mucosa without a distinct glandular pattern (fig 6 *c*). Some of these cells are unusually large, most have deeply chromatic nuclei, and a few are multinucleated. At no point in any of the sections is there demonstrable invasion of the submucosa. In this same case atypical cells are scattered throughout the submucosa, the muscularis and the serosa. These cells (fig 5 *d*) are relatively large and contain material which takes the mucicarmine stain. They have been tentatively identified as mesenchymal in type.

The occurrence of chronic gastritis and gastric carcinoma together suggests a possible relation between the two conditions. At the present time any thought regarding the causation of cancer of the stomach is largely speculative. Many investigators, however, particularly Konjetzny,<sup>2</sup> have expressed the belief that carcinoma never develops in perfectly normal gastric mucosa. They suggested that chronic gastritis is of considerable importance as a basis for carcinoma of the stomach. It is the experience of these investigators that gastric carcinoma is always associated with a pronounced gastritis with either atrophic or atrophic-hypertrophic mucosa.

It must be admitted that “carcinoma *in situ*” is not an outspoken invasive tumor, but it can be considered as a type of preinvasive carcinoma of the stomach. The time at which invasion may begin is, of course, impossible to tell, and it may be a few months or many years. The simultaneous occurrence of chronic gastritis and this noninvasive carcinoma may indicate a relation between the two. There is, of course, a stage in the development of every large carcinoma in which there are only a few malignant cells in the mucosa. Carcinoma *in situ* is thought to be such a lesion. It might thus be the intermediate stage between chronic inflammation of the stomach and outspoken gastric carcinoma.

Chronic gastritis is of utmost importance because of its possible relation to gastric carcinoma.<sup>9</sup> This is readily seen in studies of the

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9 Schindler, R. Early Diagnosis of Cancer of the Stomach. *Gastroscopy and Gastric Biopsies, Gastrophotography, and X-Rays*, J Nat Cancer Inst 1 451 (Feb) 1941. Konjetzny.<sup>2</sup>



statistics of the cure of gastric carcinoma with present methods of diagnosis and therapy. According to Pack and Livingston,<sup>10</sup> three year cures are obtained in 32 per cent, five year cures in 19 per cent and ten year cures in 07 per cent of all cases of gastric carcinoma (both operable and inoperable). In other words, five year cures are obtained in less than 2 of every 100 patients with gastric carcinoma who enter a hospital, in spite of modern surgical treatment. These figures, of course, include many cases of far advanced carcinoma which is inoperable, and certainly when resection of the involved portion of the stomach is feasible, the percentage of five year cures is considerably greater (as high as 20 per cent in some clinics).

One of the reasons for the lack of success in the treatment of this disease is the inability to recognize early stages in spite of the modern methods of diagnosis, which include gastroscopic and roentgen examinations. With present knowledge it must be admitted that a diagnosis of carcinoma *in situ* even with local mucosal invasion can probably never be made by these methods. But there must be even in the most malignant tumors an intermediate stage between the preinvasive or early invasive lesion and the large tumor mass which it would be possible to locate by gastroscopic or roentgen examination. The recognition of such early lesions of minimum size seems at the present time to be the only possible hope for those persons who might eventually be victims of gastric carcinoma.

It is an accepted fact that gastric carcinoma is more likely to develop in patients with chronic gastritis, particularly the atrophic type, than in other healthy adults. It is hoped that the careful follow-up of patients having chronic gastritis, with frequently repeated roentgen and gastroscopic examinations, may lead to the recognition of early carcinomas of minimum size that have not yet invaded lymphatics and have not caused recognizable symptoms. The diagnosis and the surgical treatment of such early carcinomas would in all probability increase the percentage of cures in carcinoma of the stomach.

#### CONCLUSIONS

Five cases of chronic gastritis simulating carcinoma are reported.

Chronic gastritis in itself may be a serious disease. In some cases it causes pyloric obstruction and may require surgical resection.

The symptoms, signs and roentgen and gastroscopic appearance and even the gross appearance of the stomach are in many instances like those of gastric carcinoma.

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<sup>10</sup> Pack, G. T., and Livingston, E. M. Treatment of Cancer and Allied Diseases, New York, Paul B. Hoeber, Inc., 1940, vol. 2.

Chronic gastritis may be, at least in some instances, a curable pre-cancerous condition. Carcinoma *in situ* may be considered as a curable preinvasive stage of cancer.

Chronic gastritis is of importance because of its possible relation to gastric carcinoma. Patients with this condition should be carefully followed up with repeated roentgen and gastroscopic examinations to discover, if possible, gastric carcinoma in its early stage and thus increase the percentage of surgical cures of carcinoma of the stomach.

University Hospitals

# INDUCED THIAMINE (VITAMIN B<sub>1</sub>) DEFICIENCY IN MAN

RELATION OF DEPLETION OF THIAMINE TO DEVELOPMENT OF  
BIOCHEMICAL DEFECT AND OF POLYNEUROPATHY

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In the first study of isolated thiamine deficiency, which Smith and two of us (R D W and H L M<sup>1</sup>) made in 1939, 4 young women were maintained on a basal diet which provided 0.15 mg of thiamine per day (0.075 mg per thousand calories of the diet) for 147 days. Vitamin A, vitamin D, ascorbic acid (vitamin C), niacin (nicotinic acid), riboflavin, iron and calcium were provided as supplements to this diet. The study of severe restriction of thiamine was repeated in 1940 with 4 young women who were maintained on the same basal diet for 88 days.<sup>2</sup> In the later study vitamins of the B complex, other than thiamine, were provided by administration of 20 Gm of autoclaved brewers' yeast per day. This yeast after autoclaving did not contain any thiamine. Its content of the other factors of the vitamin B complex was less severely affected by autoclaving. Twenty grams of autoclaved yeast contained (by analysis) approximately 1.0 mg of riboflavin, 0.8 mg of pyridoxine and 0.6 mg of pantothenic acid. Two additional subjects, serving as controls, received the same diet supplemented with thiamine hydrochloride, as well as with the autoclaved yeast.

The abnormalities ultimately noted in all the subjects who thus were severely deprived of thiamine for several weeks were depressed mental

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From the Division of Biochemistry, Mayo Foundation (Drs Mason and Power), and the Division of Medicine, Mayo Clinic (Dr Wilder)

1 Williams, R D, Mason, H L, and Smith, B F. Induced Vitamin B<sub>1</sub> Deficiency in Human Subjects, Proc Staff Meet, Mayo Clin **14** 787-793 (Dec 13) 1939

2 Williams, R D, Mason, H L, Wilder, R M, and Smith, B F. Observations on Induced Thiamine (Vitamin B<sub>1</sub>) Deficiency in Man, Arch Int Med **66** 785-799 (Oct) 1940

states, paresthesias, generalized weakness, giddiness, backache, soreness of muscles, palpitation and precordial distress (pseudoangina) on exertion, insomnia, anorexia, nausea, vomiting, loss of weight, atony of muscles, faint heart sounds, lowered blood pressures and bradycardia when the subject was at rest in bed, with tachycardia and sinus arrhythmia on exertion. In all cases, physical activity was greatly decreased and capacity for work fell progressively during the period of restricted intake of thiamine. Electrocardiographic abnormalities developed, and evidence of impairment of gastrointestinal motility was provided by roentgenograms which were taken at intervals after ingestion of a barium sulfate meal. Values for concentration of bisulfite-binding substances, which included pyruvic acid, and for lactic acid in the blood were elevated, irregularly before, but particularly after, exercise and after administration of dextrose. None of these signs and symptoms was observed in the control subjects so long as the intake of thiamine exceeded 0.45 mg per thousand calories. In general, severe restriction of thiamine was associated ultimately with states of inactivity, apathy, derangement of metabolic processes, loss of weight and prostration.

In a second study<sup>3</sup> the intake of thiamine was restricted less severely. The basal diet, composed of foods commonly appearing on American tables, provided 0.45 mg of thiamine per day (0.22 mg per thousand calories). Again, the basal diet was supplemented with minerals, vitamin A, vitamin D, ascorbic acid and autoclaved brewers' yeast and, therefore, it was deficient, so far as could be judged, only in thiamine. The study, beginning July 25, 1940 and ending June 1, 1941, was divided into a foreperiod during which thiamine hydrochloride was administered, a period of restriction of thiamine and an after-period during which thiamine hydrochloride was again administered, the subjects being maintained continuously on the basal diet. Therefore, each subject served as her own control. Eleven subjects were employed in this study. Six of them, after a period of preliminary restriction of thiamine, received thiamine hydrochloride in increasing amounts for the purpose of study of thiamine requirements. This group of 6 subjects served in some degree as controls for the group of 5 subjects who were deprived of thiamine for periods as long as 196 days. In this study moderate, prolonged restriction of thiamine, but not of calories, was associated with states of emotional instability, reflected by irritability, moodiness, quarrelsomeness, lack of cooperation, vague fears progressing to agitation, mental depression, variable restriction of activity and numerous somatic complaints. Detectable metabolic disturbances, occurring irregularly, were of variable degree of severity and were reflected in disturbance of function of various

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3 Williams, R. D., Mason, H. L., Smith, B. F., and Wilder, R. M. Induced Thiamine (Vitamin B<sub>1</sub>) Deficiency and the Thiamine Requirement of Man. Further Observations, *Arch. Int. Med.* **39**: 721-738 (May) 1942.

tissues of the body. None of these signs, symptoms or metabolic defects were observed in the control subjects when their intakes of thiamine exceeded 0.5 mg per thousand calories.

Neither acute, severe deprivation nor moderate, prolonged deprivation of thiamine produced the classic syndrome of beriberi which has been observed in the Orient. In severe restriction of thiamine prostration and inanition precluded continuation of deprivation just when neuropathy appeared certain of development. In prolonged moderate restriction of thiamine general impairment of mental and physical health was the predominant manifestation of deficiency disease. Therefore, it appeared likely that restriction of thiamine to a degree intermediate between 0.075 and 0.22 mg per thousand calories might induce, within a reasonable period, the syndrome of beriberi. The recent studies of Swank and Bessey<sup>4</sup> of avian thiamine deficiency indicated that less severe restriction of thiamine or periodic administration of small doses of thiamine enabled pigeons to live until polyneuropathy developed. Likewise, we believed that the procedure of "partial periodic cure" would serve to maintain a more satisfactory level of activity and to restore the flagging appetite of the subject. Therefore, in a third study, reported here, a diet was constructed so that it provided 0.1 mg of thiamine per thousand calories, which would be increased to approximately 0.175 mg per thousand calories by periodic administration of small doses of thiamine hydrochloride. Adoption of this method of study also enabled us to determine periodically the excretion of a test dose of thiamine, which was a second purpose of the study.

Our earlier studies clearly indicated that the ordinary excretion of thiamine for twenty-four hours reflected closely the current intake of thiamine. They also showed that excretion after subcutaneous administration of a test dose of 1.0 mg of thiamine hydrochloride reflected closely the "apparent" stores of thiamine in the tissues. Two of us (H. L. M. and R. D. W.) have discussed the significance of tests of excretion in another paper.<sup>5</sup>

Since 1939 we have accumulated data on the content of pyruvic acid, lactic acid, bisulfite-binding substances and dextrose in the blood after exercise and after administration of various carbohydrates, such as dextrose, lactate, pyruvate, levulose and sucrose, in normal and in thiamine-deficient subjects. Details of the accumulated data will be presented later. Suffice it to state here that determinations of pyruvic acid, lactic acid and dextrose in the blood after oral or intravenous administra-

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4 Swank, R. L., and Bessey, O. A. Avian Thiamine Deficiency: Characteristic Symptoms and Their Pathogenesis, *J. Nutrition* **22** 77-89 (July) 1941.

5 Mason, H. L., and Williams, R. D. The Urinary Excretion of Thiamine as an Index of the Nutritional Level: Assessment of the Value of a Test Dose, *J. Clin. Investigation* **21** 247-255 (March) 1942.

tion of dextrose appear to be the most reliable and generally applicable of the several test procedures which we have used for estimation of probable severity of the metabolic defect in states of thiamine deficiency, uncomplicated by other states of disease. The data indicate that in states of thiamine deficiency the values for pyruvic acid and lactic acid in the blood are abnormally elevated, infrequently when the subject is in the basal postabsorptive state or at rest in bed, but regularly after administration of dextrose.

We have selected the following procedures for the tests, which are performed with the subject in the basal state. For the intravenous test 0.4 Gm of dextrose (0.8 cc of 50 per cent solution of dextrose) per kilogram of body weight is injected intravenously in three minutes. Samples of blood for analysis of content of pyruvic acid,<sup>6</sup> lactic acid<sup>7</sup> and dextrose are taken just before injection and at thirty, sixty and one hundred and twenty minutes after injection. The value for pyruvic acid and for lactic acid at thirty minutes is most significant. This intravenous test is made when nausea prevents administration by mouth. Otherwise an oral test is used. For the oral test, 50 Gm of dextrose in 250 cc of solution is administered and thirty minutes later another 50 Gm of dextrose is given, as in a dextrose tolerance test as performed by Exton and Rose.<sup>8</sup> Samples of blood for analysis are taken just before administration of the first dose of dextrose and at thirty, sixty and ninety minutes after administration of the first dose. The values for pyruvic acid, lactic acid and dextrose obtained at sixty and ninety minutes are most significant. An earlier detection of the state of thiamine deficiency is possible with this larger "metabolic load" test of 100 Gm of dextrose. Division of the total dose of dextrose has reduced the incidence of emesis, a frequent complication of the test in thiamine deficiency. In general, the higher values for pyruvic acid have been encountered in the more severe states of thiamine deficiency. The general nature of the accumulated data of the dextrose tolerance tests is indicated in figures 1 and 2 and in table 1.

The "metabolic load" test is not a specific test for thiamine deficiency, and unless it is performed with the subject in the basal state, results of the test cannot be interpreted with any degree of precision. For example, we found that administration of dextrose to a person suffering from "total" diabetes was not associated with a rise of pyruvic acid in the blood.

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6 Beuding, E., and Wortis, H. The Stabilization and Determination of Pyruvic Acid in the Blood, *J Biol Chem* **133** 585-591 (April) 1940.

7 Barker, S. B., and Summerson, W. H. The Colorimetric Determination of Lactic Acid in Biological Materials, *J Biol Chem* **138** 535-554 (April) 1941.

8 Exton, W. G., and Rose, A. R. Diabetes as a Life Insurance Selection Problem, *Proc A Life Insur M Dir America* (1931) **18** 252-273. Matthews, M. W., Magath, T. B., and Berkson, J. The One Hour-Two Dose Dextrose Tolerance Test (Exton-Rose Procedure). Diagnostic Significance, *J A M A* **113** 1531-1537 (Oct 21) 1939.

unless insulin had been administered previously Administration of dextrose to a subject who had "alimentary glycosuria" was associated with abnormally high values for pyruvic acid Administration of dextrose to subjects who had states of hypermetabolism, induced by administration of desiccated thyroid, was associated with abnormal elevations of pyruvic acid in the blood Presumably in the case of diabetes mellitus either the rates of removal of pyruvic acid and lactic acid were increased or their rates of formation considerably decreased at the blood sugar levels studied (200 to 600 mg per hundred cubic centimeters of blood) In the cases of induced hypermetabolism the values for dextrose in the blood did not reach abnormal heights, and therefore, the high values for pyruvic acid were caused by either unusual rapidity of mobilization of

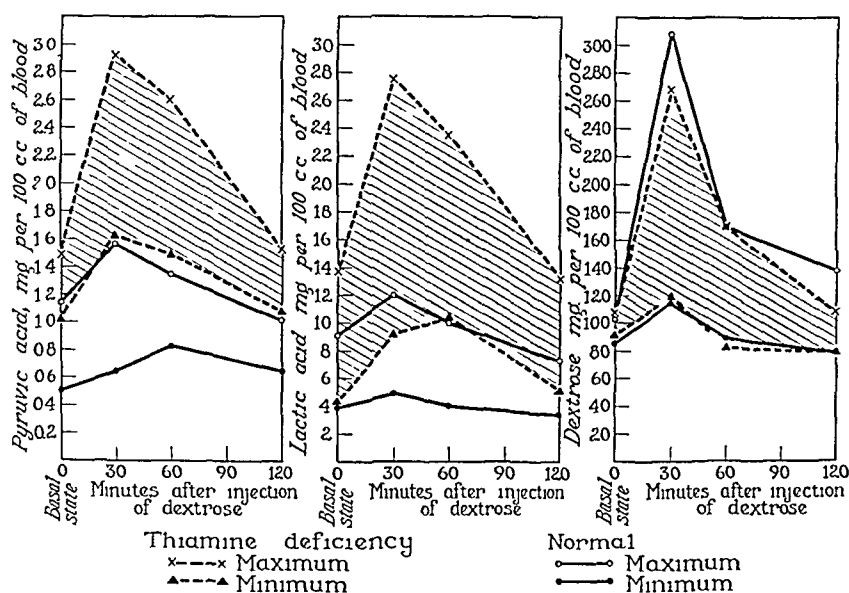


Fig 1—The range of values for pyruvic acid, lactic acid and dextrose in the blood after intravenous administration of dextrose (0.4 Gm of dextrose per kilogram of body weight in three minutes) Data for "normal" were obtained in studies on 12 physically normal subjects who were known to have been well supplied with thiamine and otherwise received the same nutrients as the thiamine-deficient subjects Data for "thiamine deficiency" were obtained in studies on 7 subjects who had been maintained for periods of various duration on standard diets which provided either 0.1 or 0.2 mg of thiamine per thousand calories and who, therefore, were known to be in states of thiamine deficiency

intermediary metabolites or abnormally slow rates of utilization of the metabolites

#### METHODS

The subjects for this, as for our previous investigations of thiamine restriction, were chosen from among inmates of a large hospital for psychopathic persons They had "recovered" from acute phases of mental illness and were able to exercise an informed decision in volunteering for this service The consent of nearest of kin and of guardians was also obtained In the present study a group of several

women received an ample diet for a period of 52 days, whereby a good nutritional status could be assured. During this time they became familiar with ward routines and analytic procedures and were observed closely. After this period of preliminary observation 2 of the group were selected for the study reported here. The final selection was made on the basis of willingness and ability to cooperate, absence of evidence of abnormal nutrition and absence of significant physical or emotional abnormality. The subjects, under close observation, continued to be engaged in activities of the ward, such as housekeeping and laundering.

The basal diet was arranged to provide not more than 0.1 mg of thiamine for each 1,000 calories. The variety of foods necessarily was limited. They were white flour, sugar, tapioca, corn starch, polished rice, raisins, egg white, cottage cheese, American cream cheese, butter, hydrogenated fat, tea and cocoa. Samples

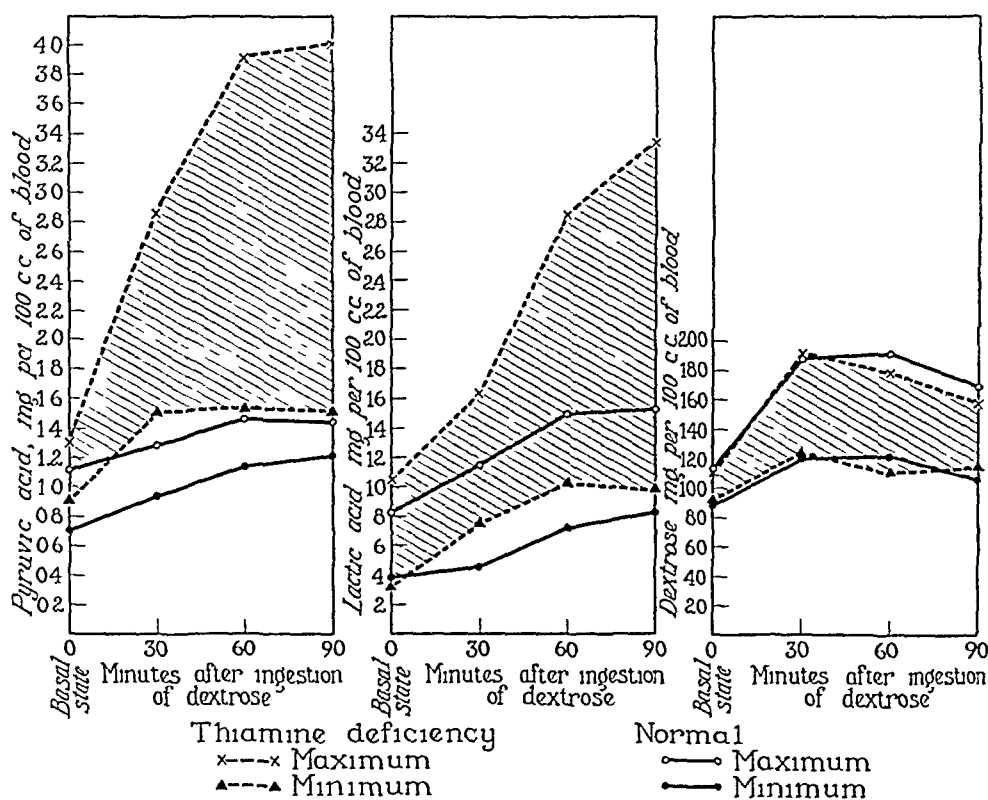


Fig 2—The range of values for pyruvic acid, lactic acid and dextrose in the blood after oral administration of dextrose (50 Gm dextrose in 250 cc of solution at zero time and 50 Gm at thirty minutes). Data for "normal" were obtained in studies on 11 physically normal subjects who were known to have been well supplied with thiamine and otherwise received the same nutrients as the thiamine-deficient subjects. Data for "thiamine deficiency" were obtained in studies on 10 subjects who had been maintained for periods of various duration on standard diets which provided either 0.1 or 0.2 mg of thiamine per thousand calories. Thus, these subjects were known to be in states of thiamine deficiency.

of the individual foods, as well as samples of the composite diet, were analyzed for their content of thiamine. The analysis for thiamine was made by the method of Hennessy<sup>9</sup>. The basal diet contained approximately 250 Gm of carbohydrate,

<sup>9</sup> Hennessy, D. J. Chemical Methods for the Determination of Vitamin B<sub>1</sub>. *Indust & Engin Chem (Analyt Ed)* **13** 216-218 (April 15) 1941.



TABLE 1—*Concentration of Pyruvic Acid, Lactic Acid and Dextrose in the Blood After Intravenous Administration of Dextrose at Intervals During Development of Thiamine Deficiency*

Period of Restriction of Thiamine, Days	Urinary Excretion of Thiamine in 24 Hours, Micrograms	Urinary Excretion of Test Dose of 1 Mg of Thiamine Hydrochloride in 4 Hours, Micrograms	Clinical Estimate of Degree of Deficiency State*	Concentration at Given Intervals After Administration of Dextrose, Mg per 100 Cc of Blood									
				Pyruvic Acid			Lactic Acid			Dextrose			
				Basal State	30 Minutes	60 Minutes	Basal State	30 Minutes	60 Minutes	Basal State	30 Minutes	60 Minutes	120 Minutes
				Subject 1	A Woman Aged 36, 168 Cm Tall, Weighing 53.5 Kg			Subject 2	A Woman Aged 48, 161 Cm Tall, Weighing 55 Kg				
0	480	538	0	0.7	0.9	1.1	0.7	0.7	0.7	0.7	0.7	0.7	0.7
33	10	113	1	0.8	1.4	1.2	0.8	0.8	0.8	0.8	0.8	0.8	0.8
65	6	64	2	1.2	1.8	1.6	1.1	0.9	0.9	0.9	0.9	0.9	0.9
83	14	13	3	0.9	2.2	1.8	1.0	0.7	0.7	0.7	0.7	0.7	0.7
110	8	39	4	1.5	3.2	2.6	1.5	0.8	0.8	0.8	0.8	0.8	0.8
Subject 2 A Woman Aged 48, 161 Cm Tall, Weighing 55 Kg													
0	450	548	0	0.8	1.3	1.2	0.7	0.7	0.7	0.7	0.7	0.7	0.7
35	10	96	1	1.0	1.5	1.2	1.0	0.6	0.6	0.6	0.6	0.6	0.6
63	12	74	2	1.2	2.3	1.9	0.9	0.7	0.7	0.7	0.7	0.7	0.7
83	11	58	3	1.0	2.0	2.2	1.0	0.6	0.6	0.6	0.6	0.6	0.6
110	6	37	4	1.2	2.3	2.1	1.1	0.5	0.5	0.5	0.5	0.5	0.5

\* 1, minimal state of thiamine deficiency, 2, moderately advanced state, 3, far advanced state, and 4, anatomic defect

60 Gm of protein and 90 Gm of fat. The caloric intake was adjusted to the requirement of each subject by giving fractions or multiples of the standard diet. By this procedure the ratio of thiamine to calories was maintained nearly constant. The diet was supplemented with 0.2 Gm of halibut liver oil fortified with irradiated ergosterol (0.2 Gm of which provided 10,000 international units of vitamin A and 4,000 international units of vitamin D), 120 mg of ascorbic acid, 10 mg of riboflavin, 20 mg of pyridoxine, 50 mg of calcium pantothenate, 200 mg of nicotinic acid amide, 0.25 Gm of choline chloride, 0.2 Gm of inositol, 0.2 Gm of ferrous sulfate and 0.6 Gm of tricalcium phosphate<sup>10</sup>. Iodized table salt (sodium chloride) was used in the preparation of the diet.

Excretion of thiamine for twenty-four hours was determined once each week, and excretion of the test dose of 10 mg of thiamine hydrochloride administered subcutaneously was determined approximately every two weeks. The test dose was administered to the subject in the postabsorptive state, and urine was collected for four hours after the injection. As has been stated, this periodic administration of the test dose raised the average intake of thiamine to approximately 0.175 mg per thousand calories. Content of pyruvic acid, lactic acid and dextrose in the blood after intravenous administration of dextrose, as previously described, body weight, physical and neurologic signs, electrocardiographic changes, motility of the gastrointestinal tract as estimated by roentgen examination, blood counts, serum protein and basal metabolic rates had been determined during the period of preliminary observation. They were determined at intervals during the period of deprivation of thiamine and again during the period in which the basal diet, deficient in thiamine, was supplemented with thiamine hydrochloride. Needless to say, the carrying out of observations of this nature entailed unusual cooperation of nursing and dietary assistants. This work was made possible by the assistance of Miss Margaret Pewters, Miss Phyllis Newman, Mrs. H. H. Pattinson, Miss Fern Dahlgren and Miss Jane Spence.

#### OBSERVATIONS ON SUBJECTS WHILE THEY WERE RECEIVING THE DIET DEFICIENT IN THIAMINE

The period of restriction of thiamine began Sept. 23, 1941 and ended Jan. 20, 1942 (120 days). Deprivation of thiamine was discontinued because in case 1 a severe neurologic defect had developed and in case 2 less severe, but nevertheless definite, signs of neurologic defects had appeared. The appetites of both subjects had failed, and inanition seemed imminent.

The intake and excretion of thiamine, the intake of food and data on values for pyruvic acid after intravenous administration of dextrose are presented in figures 3 and 4. Data on excretion of thiamine after injection of a test dose of thiamine hydrochloride (an index of the depletion of tissue stores of thiamine), values for pyruvic acid and lactic acid after administration of dextrose (a suggestive index of severity of biochemical defect), the activity of the patellar and the achilles tendon reflexes and ability of the subject to rise from the squatting position (suggestive indexes of neurologic damage) are summarized in tables

<sup>10</sup> Dr. D. F. Robertson, Associate Medical Director, Merck and Company, Inc., Rahway, N. J., supplied us with thiamine hydrochloride, riboflavin, pyridoxine, calcium pantothenate and choline chloride.

2 and 3 The clinical courses of the 2 subjects during the development of thiamine deficiency are presented in greater detail later in the reports of progress of subjects. Details of the responses of the patients to treatment with thiamine hydrochloride will be presented in another article. It suffices to state here that administration of 60 to 80 mg of thiamine hydrochloride both orally and parenterally corrected, in part, the gross biochemical defect within a week. Appetite, strength (in the absence of paralysis) and feeling tone had improved greatly by the seventh day and had returned to the norm for the subject within thirty days. However, the more severe neurologic defects in case 1 were not fully corrected by inten-

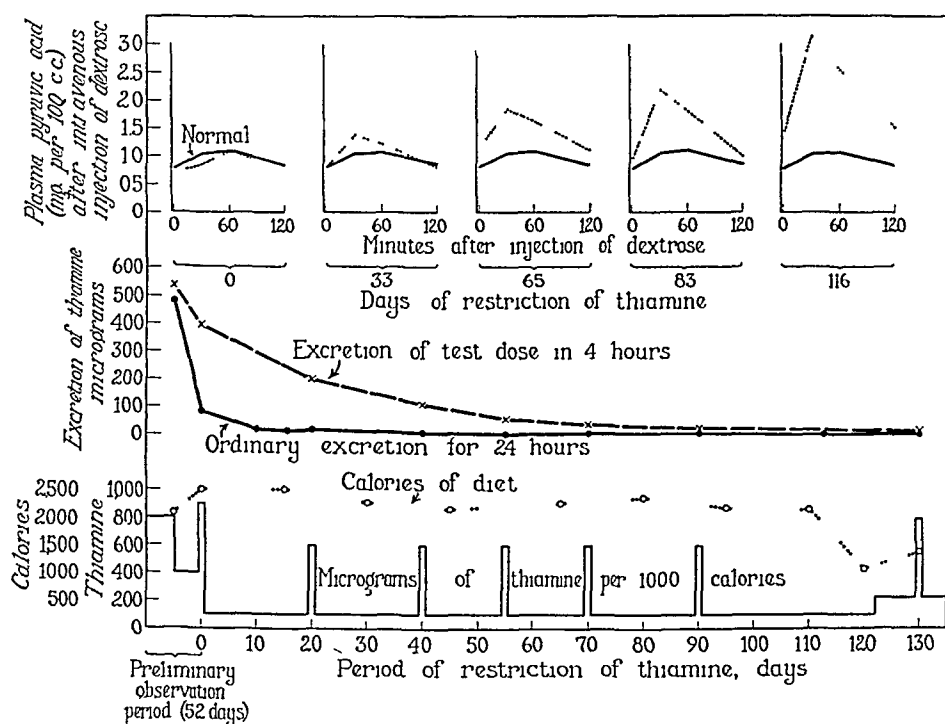


Fig 3 (case 1)—Intake and excretion of thiamine, excretion of a test dose of thiamine (10 mg thiamine hydrochloride was injected subcutaneously, the excretion in four hours after injection was determined, the subject was fasting), and data on pyruvic acid in the whole blood (not plasma as indicated in the figure) after intravenous administration of dextrose. The data for the top row of figures are taken from table 1.

sive treatment with thiamine hydrochloride for 120 days, although movements of extension, flexion, abduction and adduction of the thighs and legs had become progressively stronger. The achilles tendon and the patellar reflexes in case 1 remained absent after 121 days of treatment. The less advanced neurologic defects in case 2 were corrected by intensive treatment (15 mg of thiamine hydrochloride per day) for 60 days.<sup>10a</sup>

10a The subject of case 1 was reported Dec 15, 1942 to have recovered normal strength in the muscles previously affected.

## REPORTS OF PROGRESS OF SUBJECTS

**CASE 1**—The subject was an active, vigorous and industrious woman aged 36, 168 cm tall and weighing 56.5 Kg. She had been engaged for several months in laundering. Her cooperation in the matter of eating and, so far as her strength would permit, in working was entirely satisfactory. The clinical course of this subject was not complicated by intercurrent infections. Body temperatures were not observed to be abnormal at any time.

**Observations at 30 Days**—Anorexia had developed. The subject was weak and thereafter voluntarily restricted the duration and vigor of her activities.

**Observations at 50 Days**—The subject complained of nausea and epigastric distress and vomited occasionally after meals. The values for pyruvic acid in the blood after administration of dextrose were abnormally high.

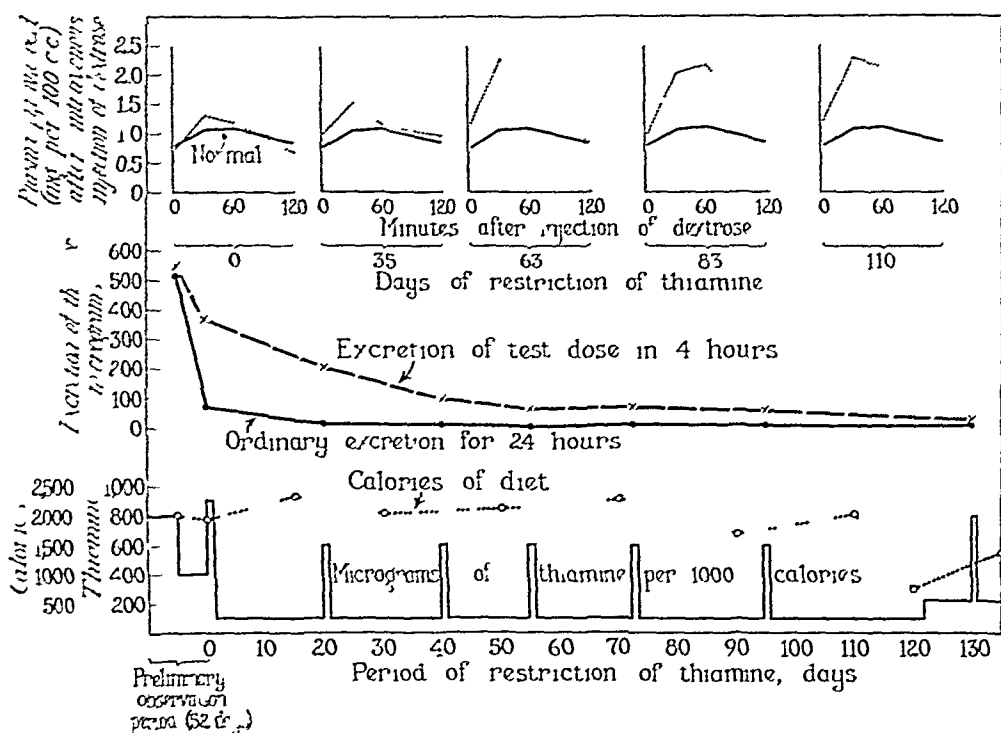


Fig 4 (case 2)—Intake and excretion of thiamine, excretion of a test dose of thiamine (10 mg of thiamine hydrochloride was injected subcutaneously, the excretion in four hours after injection was determined, the subject was fasting), and data on pyruvic acid in the whole blood (not plasma as indicated in the figure) after intravenous administration of dextrose. The data for the top row of figures are taken from table 1.

**Observations at 70 Days**—Nausea was constantly present, weakness was severe. The subject limited her activities to assisting with the lighter duties of the ward and frequently did not complete the tasks. She was apathetic and confused and at times made complaints of numbness and tingling (paresthesia) of the medial surfaces of the legs from the knees to the ankles.

**Observations at 90 Days**—Spontaneous exertions had almost ceased, interest in reading was conspicuously absent. Interpretation of the stimulus of a wisp of cotton and of a pinprick applied to areas on the medial surfaces of the legs was inaccurate. Muscles of the calves of the legs were tender and ability to rise

from the squatting position was definitely impaired. The patellar reflexes were slightly hyperactive, the achilles tendon reflexes were hypoactive.

*Observations at 110 Days*—The appetite had failed, apathy, vagueness and confusion were conspicuous. The blood pressure was 100 mm of mercury systolic and 65 mm diastolic, the cardiac rate was variable but usually slow (55 to 65 beats per minute) during rest in bed and rapid (90 to 120 beats per minute) on ordinary exertions. The heart sounds were faint. Application of a wisp of cotton

TABLE 2—*Development of Biochemical Defect of Thiamine Deficiency in Subject 1\**

Day of Period	Excretion of Thiamine in 24 Hr, Micro grams	Excretion of Test Dose of 1 Mg of Thiamine Hydrochloride in 4 Hr, Micro grams	Thirty Minutes After Administration of Dextrose, Mg per 100 Cc		Patellar Tendon Reflex†	Achilles Tendon Reflex†	Ability to Rise from Squatting Position†	Symptoms or Signs Which Were Persistent
			Pyruvic Acid	Lactic Acid				
Period of Preliminary Observation								
52	480	538	0.86	11.9	0	0	0	None
Period of Restriction of Thiamine								
10	19	200			0	0	0	None
30	10	113	1.38	14.9	0	0	0	Anorexia, weakness
50	6	64			0	0	-1	Nausea, weakness, epigastric pain
70	11	101	1.84	18.7	0	0	-1	Nausea, weakness, sensation of numbness below knees
90	14	13	2.18	15.4	+2	-1	-2	Weakness, giddiness, occasional emesis, sensation of numbness below knees
110	10	20			-3	-4	-3	Frequent emesis, extreme weakness, apathy, frequent stumbling, sense of touch and vibration impaired below knees
120	8	39	3.19	15.6	-4	-4	-4	Loss of weight, mental confusion, prostration, sense of touch and vibration impaired at knees and ankles, paralysis of quadriceps femoris
Period of Intensive Treatment with Thiamine Hydrochloride ‡								
10			1.48	11.0	-4	-4	-4	Return of appetite, no further loss of weight, less mental confusion, paralysis of quadriceps femoris
30			1.35	13.0	-4	-4	-4	Good appetite, gain in weight, less mental confusion, return of interest, paralysis persistent

\* A woman aged 36, 168 cm tall, weighing 56.5 kg.

† 0, normal, and -4, absent.

‡ More than 60 mg of thiamine hydrochloride per day.

and pinprick to the medial surfaces of the legs evoked delayed and inaccurate responses. The vibratory sense at the knees and ankles was impaired but not absent. Although a defect of the sense of active or passive position of the knee and ankle joints could not be demonstrated with any degree of certainty, the subject walked with little flexion of the knees and frequently stumbled. She could rise from the squatting position only with some assistance but could stand on her heels and toes and on one foot. Up to the one hundred and tenth day there had been a slight gain of weight (3.8 Kg), but during the ensuing 10 days a loss of weight (2.7 Kg) occurred.

*Observations at 120 Days*—The data of several examiners<sup>11</sup> indicated that acuity of perception of touch, pain and two points was impaired, with response delayed, over the medial surface of the thighs and especially the legs, but that appreciation of differences of temperature was not impaired over the same area or elsewhere. Sense of vibration was impaired at the ankles but not at the knees. Sense of position of the joints of the toes and legs was not impaired. Movements of abduction, adduction and flexion of the thighs and legs were weak. Extension of the legs, involving chiefly the quadriceps femoris muscles, was barely per-

TABLE 3—*Development of Biochemical Defect of Thiamine Deficiency in Subject 2\**

Day of Period	Excre- tion of Thia- mine in 24 Hr, Micro grams	Test Dose of 1 Mg of Thiamine Hydro- chloride in 4 Hr, Micro grams	Thirty Minutes After Administration of Dextrose, Mg per 100 Cc		Patellar Tendon Reflex†	Achilles Tendon Reflex†	Ability to Rise from Squat- ting Posi- tion†	Symptoms or Signs Which Were Persistent
			Pyruvic Acid	Lactic Acid				
Period of Preliminary Observation								
52	450	548	1.36	7.9	0	0	0	None
Period of Restriction of Thiamine								
10	15	194			0	0	0	None
30	10	96	1.50	9.6	0	0	0	Anorexia, weakness
50	5	73			0	0	-1	Nausea, epigastric pain, con- stipation, weakness
70	12	74	2.26	19.6	0	0	-2	Nausea, weakness, apathy inactivity
90	11	58	2.00	16.6	+2	+1	-2	Nausea, occasional emesis, inactivity, mental confusion
110	8		2.27	17.0	-1	-2	-3	Aversion to food, giddiness, weakness, inactivity, pros- tration, slight impairment of sense of touch and vibration
120	3	37	2.64	17.2	-3	-3	-3	Frequent emesis loss of weight, prostration, slight impairment of sense of touch and vibration at knee and ankle
Period of Intensive Treatment with Thiamine Hydrochloride ‡								
10			1.61	8.5	-2	-3	-2	Improved appetite, no fur- ther loss of weight, in- creased strength, greater activity
30			1.18	7.8	0	0	0	Good appetite, gain of weight, return of interest, participation in housework

\* A woman aged 48, 161 cm tall, weighing 55 Kg

† 0, normal, and -4, absent

‡ More than 15 mg of thiamine hydrochloride per day

ceptible. The subject could neither stand nor walk without support. The patellar and the achilles tendon reflexes were absent, clonus could not be elicited at the knees or ankles, a Babinski reflex was not elicited.

The initial pressure of the cerebrospinal fluid was 80 mm of water. The pressure rose promptly when the jugular veins were compressed and fell promptly when pressure on the veins was relaxed. The Kolmer and the Kline reaction of the fluid was negative, the Nonne-Apelt reaction was negative, the colloidal gold (Lange) reaction was interpreted as 000 000 000 0, and there was 1 small lymphocyte per cubic millimeter of fluid. There were, per hundred cubic centi-

11 Dr H W Woltman and Dr J R Campbell made a neurologic examination at this date.

meters of fluid, 20 mg of protein, 63 mg of sugar, 710 mg of chloride and 126 mg of pyruvic acid

**CASE 2**—The subject was an inactive woman aged 48, 161 cm tall and weighing 55 Kg. In contrast to the subject in case 1 she was neither vigorous nor industrious. Although sedentary in her habits, she assisted with the lighter tasks of housework. Her cooperation in eating and in working, after the first few weeks of deprivation, was poor. Weakness and anorexia were experienced at about the thirtieth day, and thereafter it required considerable persuasion to maintain caloric intake and activity at satisfactory levels.

*Observations at 50 Days*—The concentration of pyruvic acid in the blood after injection of dextrose was abnormally high. Complaints of anorexia were continuous, emesis was observed occasionally.

*Observations at 70 Days*—The values for pyruvic acid after injection of dextrose had become considerably higher, and emesis after meals had become a more frequent occurrence. Complaints were of nausea, epigastric pain, constipation, weakness and giddiness.

*Observations at 90 Days*—Apathy, mental confusion and inactivity had become more conspicuous. There was some tenderness of the muscles of the calves, but the subject could rise from the squatting position without assistance.

*Observations at 110 Days*—Severe nausea with frequent emesis after meals associated with epigastric pain and a high degree of generalized muscular weakness was observed. The blood pressure was 95 to 105 mm of mercury systolic and 60 to 72 mm diastolic. The cardiac rate at times of rest in bed was slow (50 to 70 beats per minute), changing after moderate exertion to 100 to 120 beats per minute. Complaints were made of numbness and tingling of the antero-medial surfaces of the thighs and legs. Interpretations of stimuli, such as a wisp of cotton, pinprick and warm and cool tubes, were essentially accurate, although responses to stimuli were delayed considerably. Impairment of the sense of vibration and of the sense of position could not be demonstrated. The subject could stand on her heels and toes and on one foot, but rising from the squatting position was accomplished only with some assistance. The achilles tendon and the patellar reflexes were somewhat hyperactive but clonus could not be elicited at the ankle or knee. A Babinski sign was not elicited.

Deprivation of thiamine up to the one hundred and tenth day had been associated with a slight gain of weight (23 Kg), but in the ensuing 10 days, the appetite failed and there was a loss of 27 Kg. There was a rapid progression of the apathy and weakness. Emesis became frequent and severe.

*Observations at 120 Days*—The blood pressure was 90 to 98 mm of mercury systolic and 50 to 60 mm diastolic, the cardiac rate at rest in bed was slow (58 to 68 beats per minute), there was marked sinus arrhythmia, and pallor and giddiness were observed with changes from the recumbent to the erect position. The subject walked with little flexion of her knees and occasionally stumbled. Inattention on her part made for difficulty in interpretation of the data of the sensory examination. The responses to the stimulus of a wisp of cotton and of a pinprick, applied below the knees, were always delayed, uncertain and frequently inaccurate. A defect of the sense of position of the legs and toes could not be elicited, the sense of vibration was impaired but not absent at the ankles. Standing on heels and toes and on one foot was done with much swaying. Rising from the squatting position could be accomplished only with assistance. The patellar tendon reflexes were hypoactive but could be obtained with Jendrassik

reinforcement, the achilles tendon reflexes were absent. A Babinski reflex was not to be elicited.

The pressure of the cerebrospinal fluid was 140 mm of water. The pressure rose promptly when the jugular veins were compressed and fell promptly when the pressure on the veins was relaxed. The Kolmer and the Kline reaction was negative, the Nonne-Apelt reaction was negative, and the colloidal gold (Lange) reaction was read 011 100 000 0. The cerebrospinal fluid contained, per hundred cubic centimeters, 35 mg of protein, 56 mg of sugar, 749 mg of chlorides and 1.25 mg of pyruvic acid.

#### COMMENT

Evidence of deprivation of thiamine was first manifested in these 2 subjects by low levels of thiamine excreted in the urine. Evidence of some degree of deficiency of thiamine was first manifested by lower levels of excretion after administration of a test dose of thiamine hydrochloride. Almost simultaneously with significant decrease of excretion of the test dose of thiamine the values for pyruvic acid in the blood after administration of dextrose became elevated, and the subjects became listless and complained of anorexia and fatigue. Listlessness progressed to apathy, anorexia progressed to nausea and fatigue progressed to prostration, almost stepwise with the decrease of excretion of the test dose of thiamine and with elevation of the level of pyruvic acid in the blood. Symptoms suggestive of dysfunction of the central and the peripheral nervous pathways preceded by months the gross signs of neurologic dysfunction. However, after 110 days defects of the cutaneous sensory pathways, depression or disappearance of the tendon reflexes and paralysis of the muscles of the thighs and legs became apparent.

In our earlier studies of severe restriction of thiamine evidence of polyneuropathy, as manifested by loss of patellar and achilles tendon reflexes and paralysis of the quadriceps femoris muscles, was observed in only 1 of 8 subjects. At that time, mainly because the abnormality was mild, its significance in the light of the studies reported here was not appreciated. In a second study<sup>3</sup> of prolonged, moderate restriction of thiamine some degree of weakness of muscles and paresthesias of the medial surfaces of the legs were observed in subjects who were deprived of thiamine for periods of 88 to 196 days, but paralysis of muscles and loss of tendon reflexes were not observed. Reconsideration of the data of these earlier studies suggests that in the first study the restriction of thiamine was too severe for maintenance of the organism, and therefore, deprivation had to be discontinued before much neuropathy could develop, and that in the second study the restriction was not severe enough for production of objective neurologic defects within the periods of observation.

In the study here reported the dietary restriction of thiamine was intermediate, and administration at periodic intervals of approximately



two weeks of a test dose of 10 mg of thiamine hydrochloride exerted a temporary recuperative effect. Invariably appetite would be improved and activity would be resumed for 7 to 10 days after injection of the test dose.

Studies by Leblond and Chaulin-Serviniere,<sup>12</sup> reported since our observations were made, provide data which are consistent with our experience in human subjects. Using monkeys, the authors found that when the intake of thiamine was low, death would occur before any outstanding clinical symptoms of beriberi developed, whereas when the intake represented about half the minimal requirement of thiamine, clinical signs of polyneuritis, cardiac failure and at autopsy peripheral nerve degeneration were obtained.

We realize that the neuropathy which developed in our subjects might have been caused by factors which were unrelated to deprivation of thiamine. We are aware of the general belief that there are many and exceedingly obscure causes of neuropathy. However, that deficiency of thiamine was the most probable ultimate cause of the polyneuropathy in our subjects is indicated by the following considerations:

- 1 The neuropathy developed progressively in the period of isolated deprivation of thiamine and regressed when thiamine hydrochloride was provided again and no other changes were made in the regimen.

- 2 Twenty subjects, including the subjects of the present study, were maintained in the same isolated hospital ward and were served food from the kitchen in the ward. Only in those who were deprived of thiamine did polyneuropathy develop. These conditions would seem to reduce the probability that toxic or infectious factors were the cause of the neuropathies observed. We have given thought to the possibility that thiamine deficiency may have decreased the factor of resistance and thereby caused the persons who had thiamine deficiency to become oversusceptible to infectious and toxic agents. This possibility, however, seems to be excluded in a recent paper.<sup>3</sup>

- 3 Simultaneously with the present study three other groups of subjects were maintained on a basal diet deficient in all factors of the vitamin B complex and known to be low in thiamine, riboflavin and niacin. By supplementation of the basal diet with crystalline vitamins of the B complex and with minerals and other nutrients isolated deficiencies of thiamine, of riboflavin, of nicotinic acid and of the vitamin B complex have been produced. Polyneuropathy has developed only in subjects who have been deprived of thiamine.

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<sup>12</sup> Leblond, C. P., and Chaulin-Serviniere, J. Spontaneous Beriberi of the Monkey as Compared with Experimental Avitaminosis, *Am J M Sc* **203** 100-109 (Jan) 1942.

## SUMMARY

The quantity of thiamine in the diet of 2 human volunteers was restricted to 0.2 mg per day (0.1 mg for each 1,000 calories) for 120 days. A test dose of 1.0 mg of thiamine hydrochloride was administered subcutaneously approximately every two weeks during this period of thiamine deprivation, thus raising the average daily intake of thiamine to a total of 0.35 mg (0.175 mg per thousand calories). Administration of the test dose of thiamine served as a "periodic partial cure" of the thiamine deficiency. Appetite would improve and activity would increase for 7 to 10 days after each injection.

Symptoms and signs of thiamine deficiency were manifested as early as the thirtieth day of restriction. The first objective evidence of abnormality in these subjects consisted of a decrease in their ordinary urinary excretion of thiamine. At about the fiftieth day the urinary excretion of thiamine after administration of a test dose of 1 mg of thiamine hydrochloride was reduced. After this time whenever dextrose was given, abnormally high values for pyruvic acid and lactic acid in the blood were encountered. About this time, also, anorexia and weakness became more severe than they had been and the subjects made complaints of paresthesia of the legs. Later, objective evidence of dysfunction of nervous pathways was obtained, and after 110 days of restriction polyneuropathy became clearly apparent in both subjects. The neuropathy consisted of defects of the sensory nervous pathways, loss of tendon reflexes and paralysis of muscles of the legs. It responded to administration of large doses of thiamine, but only after many weeks, and in 1 case incompletely after four months of continuous treatment.<sup>10a</sup>

The earliest stages of thiamine deficiency were demonstrated by determination of excretion after administration of a test dose of thiamine hydrochloride. More advanced stages of deficiency were suggested by data on pyruvic acid and lactic acid in the blood after administration of dextrose—a "metabolic load" test. Advancing degrees of thiamine deficiency were suggested by progressively higher blood pyruvic acid curves after administration of dextrose. This metabolic load procedure has diagnostic significance in athiaminosis but cannot be regarded as specific or pathognomonic.

Polyneuropathy has been a manifestation of late rather than early, severe rather than mild, deficiency of thiamine, representing an anatomic defect which was only slowly reversible even when thiamine hydrochloride was administered intensively.

# URINARY SEDIMENT IN VISCERAL ANGIITIS (PERI- ARTERITIS NODOSA, LUPUS ERYTHEMATOSUS, LIBMAN-SACKS "DISEASE")

## QUANTITATIVE STUDIES

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In recent years many reports have appeared concerning a group of disorders featured by peculiar lesions of small arteries, namely, periarteritis nodosa, lupus erythematosus disseminata, Libman-Sacks "disease" and the syndromes described by Friedberg and Gross. The terminology used in referring to these varied conditions is much confused and is by no means certain, but some relation among them at least seems possible. In searching for a useful clinical designation for the entire group W. Dock suggested "visceral angitis," and this term has been in common use in the Stanford clinic for the past few years.<sup>1</sup>

Although the occurrence of renal lesions in association with visceral angitis is well known,<sup>2</sup> the reported studies on the urine<sup>3</sup> of

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1 My associates and I use this as a purely clinical designation, inasmuch as there are different views as to the interpretation of the lesions (see Klemperer, P., Pollack, A. D., and Baehr, G. Pathology of Disseminated Lupus Erythematosus, Arch Path **32** 569 [Oct.] 1941)

2 (a) Keil, H. Conception of Lupus Erythematosus and Its Morphologic Variants, with Particular Reference to "Systemic" Lupus Erythematosus, Arch Dermat & Syph **36** 729 (Oct.) 1937 (b) Engman, M. F., Jr. Early Acute Lupus Erythematosus, *ibid* **35** 685 (April) 1937 (c) Libman, E., and Sacks, B. A Hitherto Undescribed Form of Valvular and Mural Endocarditis, Tr. A. Am. Physicians **38** 46, 1923 (d) Gross, L., and Friedberg, C. K. Nonbacterial Thrombotic Endocarditis. Classification and General Description, Arch Int Med **58** 620 (Oct.) 1936 Friedberg, C. K., and Gross, L. Nonbacterial Thrombotic Endocarditis Associated with Acute Thrombocytopenic Purpura, *ibid* **58** 641 (Oct.) 1936 Friedman, C. K., Gross, L., and Wallach, K. Nonbacterial Thrombotic Endocarditis Associated with Prolonged Fever, Arthritis, Inflammation of Serous Membranes and Widespread Vascular Lesions, *ibid* **58** 662 (Oct.) 1936 (e) Goeckerman, W. H. Lupus Erythematosus as a Systemic Disease, J. A. M. A. **80** 542 (Feb. 24) 1923 (f) Ginzler, A. M., and Fox, T. T. Disseminated Lupus Erythematosus. A Cutaneous Manifestation of a Systemic Disease (Libman-Sacks), Arch Int Med **65** 26 (Jan.) 1940 (g) Rose, E., and Pillsbury, D. M. Acute Disseminated Lupus Erythematosus—A Systemic Disease, Ann Int Med **12** 951, 1939 (h) Symposium on Lupus Erythematosus, Proc. Staff Meet., Mayo Clin **15** 675-688, 1940 (i) Reifenshein, E. C., Reifenshein, E. C., Jr., and Reifenshein, E. C., Jr.

patients with this condition have not been adequate. A series of 21 cases encountered in the last two years has furnished an unusual opportunity to make exact quantitative studies of the urinary sediment by the methods of Addis. These studies have revealed some interesting and characteristic features of the sediment in visceral angitis, and they form the basis of this report.

#### METHOD AND MATERIAL

Specimens of urine were collected according to the method of Addis<sup>4</sup>. It may be recalled that the purpose of this procedure is to preserve the formed elements by obtaining fresh concentrated acid urine and also to estimate the total numbers of casts and cells excreted in a standard period. By this means it is possible to make an accurate assay of the nature and the course of a renal lesion. After withdrawing from a specimen the amount of urine required for the Addis count the remainder was allowed to stand in the refrigerator for two or three hours, 30 to 60 cc. was then pipetted from the bottom of the receptacle and centrifuged. The sediment, resuspended in 0.5 to 1.0 cc. of urine, was studied. The types of cells and casts were recorded, and differential counts of the casts were made.

In each of the 21 cases the disorder was given a clinical diagnosis of one or another of the components of visceral angitis already enumerated. The diagnosis was confirmed by autopsy or muscle biopsy in all but 4 cases, however, in these cases the condition was considered definite enough to permit inclusion in this series (table, group A, cases 6 and 9, group B, cases 1 and 4).

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stein, C. H. A Variable Symptom Complex of Undetermined Etiology with Fatal Termination, Including Conditions Described as Visceral Erythema Group (Osler), Disseminated Lupus Erythematosus, Atypical Verrucous Endocarditis (Libman-Sacks), Fever of Unknown Origin (Christian), and Diffuse Peripheral Vascular Disease (Baehr and Others), *Arch. Int. Med.* **63**: 553 (March) 1939. (j) Curtis, A. C., and Coffey, R. M. Periarteritis Nodosa. A Brief Review of the Literature and a Report of One Case, *Ann. Int. Med.* **7**: 1345, 1934. (k) Harris, A. W., Lynch, G. W., and O'Hare, J. P. Periarteritis Nodosa, *Arch. Int. Med.* **63**: 1163 (June) 1939. (l) Grant, R. T. Observations on Periarteritis Nodosa, *Clin. Sc.* **4**: 245, 1940.

3 (a) Bunim, J. J. Lupus Erythematosus Disseminatus, *Ann. Int. Med.* **13**: 1399, 1940. (b) Keith, N. M., and Rowntree, L. C. A Study of the Renal Complications of Disseminated Lupus Erythematosus. Report of Four Cases, *Tr. A. Am. Physicians* **37**: 487, 1922. (c) Rose, E., and Goldberg, L. C. Visceral Lesions of Acute Disseminated Lupus Erythematosus, *M. Clin. North America* **19**: 333, 1935. (d) Baehr, G., Klemperer, P., and Schiffin, A. A Diffuse Disease of Peripheral Circulation Usually Associated with Lupus Erythematosus and Endocarditis, *Tr. A. Am. Physicians* **50**: 139, 1935. (e) Snapper, I. Kidney Trouble in Acute Lupus Erythematosus, in Berglund, H., and Medes, G. *The Kidney in Health and Disease*, in Contributions by Eminent Authorities, Philadelphia, Lea & Febiger, 1935, pp. 433-439. (f) Stickney, J. M., and Keith, N. M. Renal Involvement in Disseminated Lupus Erythematosus, *Arch. Int. Med.* **66**: 643 (Sept.) 1940. (g) Klemperer, P., Pollack, A. D., and Baehr, G. Pathology of Disseminated Lupus Erythematosus, *Arch. Path.* **32**: 569 (Oct.) 1941.

4 Addis, T. A Clinical Classification of Bright's Diseases, *J. A. M. A.* **85**: 163 (July 18) 1925.

## RESULTS

Of the 21 cases, the urinary sediment was normal in 3 (table, group C) In 4 other cases the sediment was of the sort which may occur in association with any febrile illness or with arteriosclerosis (table, group B) But in 14 cases in which the diagnosis was verified and in which there was obviously a severe renal lesion a sediment of unusual type was encountered Indeed, its characteristics are so specific that once observed such sediment becomes of great diagnostic value in cases of doubtful renal disease

In order to make clear the significance of the findings in these cases of visceral angitis a brief review of the types of sediment encountered in cases of glomerulonephritis is necessary, and for the purpose of this description the disease may be divided—somewhat diagrammatically—into three active stages In the initial stage the urine contains numerous red blood cells and red cell casts The second stage, that of tubular degeneration, is characterized by the presence of fat in the urine, this fat is contained as droplets in hyaline casts and in the epithelial cells of the tubules (so-called “oval fat bodies”) Red cells are present, but during this stage red cell casts are not usually seen, for the glomerulitis has abated Large amounts of protein occur in the urine, and at the same time the concentration of protein in the serum may be low The third stage is the terminal one, in which the flow of urine is so slow in some of the large collecting tubules that large casts, known as broad, or renal failure, casts, are formed It is in this stage that hypertension and retention of urea in the blood become extreme The presence of elements characteristic of the second and the third stage has often been observed in the same specimen of urine, the presence of those typical of the initial stage and the second stage has been observed in the same specimen only extremely rarely, in cases of fulminating disease, and the presence in one sample of urine of elements characteristic of all three stages has never been observed in a case of glomerulonephritis in the experience of the Stanford laboratory

But in sharp contrast to the different sediments just outlined the urine in 14 of the 21 in this series presented in the same specimen red blood cells, red cell casts, oval fat bodies, fatty and waxy casts and, frequently, broad casts In addition, abnormal quantities of protein were always present Here, under one cover slip were seen elements characteristic of the three stages of glomerulonephritis, which are usually separated by years or decades This unique microscopic picture we have come to refer to as that of the “urine of visceral angitis” The data in these 21 cases are summarized in the table

The finding of such a singular urinary sediment in cases of typical visceral angitis became of diagnostic aid, when in later cases of atypical or obscure forms of the disease identical urinary sediments were

observed, further procedures which might otherwise have been neglected, such as muscle biopsy, were done in an attempt to confirm the diagnosis.

There is no obvious reason why this type of urinary sediment should never occur in an adult with rapidly progressing glomerulonephritis. Addis,<sup>5</sup> as a matter of fact, in reviewing his cases of glomerulonephritis found that he had encountered this picture on 2 occasions. However, his notes on these 2 cases of supposed glomerulonephritis show clearly that the patients really had disseminated lupus erythematosus. In 1 case (table group A case 14) in which the urine was typical of that of visceral angitis the necropsy report was "subacute glomerulonephritis." The condition in this case, however, was suggestive clinically of periarteritis nodosa, with prolonged fever, arthralgia, myalgia, symptoms and signs referable to the central nervous system, cough and other difficulties referable to the respiratory tract, loss of weight and at autopsy polyserositis.

An attempt was made to correlate this singular urinary sediment with the microscopic renal changes. No quantitative relation was found. As a matter of fact, the renal lesion was often less severe than one would expect from the appearance of the sediment. Sometimes only minimal changes were observed in kidneys which discharged large numbers of formed elements. Qualitatively, however, the sediment can be explained by the histologic changes, the blood casts and hematuria, by the plugging of the capillaries of the tufts by hyalinized thrombi, the epithelial and fatty casts and the oval fat bodies, by the fatty degeneration of some of the convoluted tubules, and the broad casts, by the fact that in some lobules draining into a common collecting tubule system there had been fibrosis and hyalinization of many of the glomeruli. The other lesions, the relation of which to the sediment is doubtful or nonexistent, comprised crescents and synechiae partially obliterating Bowman's capsule and the thickening of the basement membrane of the capillary loops, or formation of lesions "wire loop." It is of interest that the only really typical "wire loop" lesions were encountered in a woman (table, group A, case 1) who clinically and pathologically had periarteritis nodosa rather than disseminated lupus erythematosus. There was no constant change in the vessels supplying the renal parenchyma. In those patients with normal urine no significant renal lesions were encountered.

The changes in the urinary sediment vary with the state of the patient, becoming more extreme during clinical exacerbation and lessening during remission when its appearance may even suggest a latent stage of the renal disease. This is well illustrated by case 11, group A, after a particularly severe early phase of periarteritis nodosa the patient has improved greatly, and the changes shown in the table

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5 Addis, T. Personal communication to the author.

Quantitative Data on Urinary Sediment																				
Case Number	Age, Year	Sex	Duration of Illness	Elements in Sediment of a Twenty Four Hour Specimen of Urine																
				Casts, Millions	Types of Casts, Percentage of Total Number						Red Blood Cells, Millions	White Blood Cells and Epithelial Cells, Millions	Oval Fat Bodies, Millions	Protein, Gm	Blood Urea, Mg /100 Cc	Serum Protein, Gm /100 Cc	CO <sub>2</sub> Combining Power of Plasma, Volumes per Cent	Blood Pressure, Mm Hg	Cutaneous Lesions	
					Red Cells	Cellular Casts	Granular Casts	Waxy Casts	Hyaline and Fatty Casts	Broad Casts										
Normal limit				0.1	0	0	+	0	+	0	10	20	0	0.03						
Group A	1	24	F	7 mo	14 to 76	5 to 15	+	50	+	30	0 to 20	15 to 1,600	8 to 99	+++	12 to 60	18 to 300	?	42 to 163	118/76 to 110	0
	2	21	F	24 mo	0.2 to 8.6	0 to +++	+	+	+	+	9 to 690	5 to 1,200	0 to +	0.03 to 9.1	30 to 265	5.4	37 to 27	110/76	0	
	3	41	F	10 mo	0.8 to 3.4	10	12	25	5	+	+	12 to 295	13 to 306	6	0.3 to 2.2	27 to 115	4.9	43	176/112	-
	4	43	F	30 mo	1.4 to 2.7	10	+	+	+	+	+	180	30	+	3.8	75 to 140	6.2 to 5.2	38	155/86 to 210/120	+
	5	42	F	3 mo	2.1	30 to 40	5	30	10	5	5 to 10	7,000	1,400	+	1.7	170	4.2		125/85	0
	6	20	M	8 mo	30	+	+	+	+	+	?	82	66		2.4 to 7.9	43 to 157			145/80	+
	7	57	F	10 mo	1.4	15	+	+	+	+		560	218		2.6	66			135/80	0
	8	32	F	6 mo	1.2	6	12	12	3	67	?	420	76		5.6	86			120/70	0
	9	45	F	16 mo	5.1	6	13	24	11	42	4	47	45	1	0.5	46			145/95	0
	10	22	F	24 mo +	4.5	3	5	24	12	56		21	18	2	0.3				100/60	0
	11	39	M	18 mo +	3		+	+	+	+		525	600		4.5	140	5.3		160/100	+
					0.9	5	5					432	42	6	1.8	30	6.1		138/95	0
					0.4							28	3		0.7	31	6.88		163/125	0
																				0
	12	58	F	6 mo +	0.5	+	+		+	+	425	250		1.3	30			115/70	+	
	13	42	M	4 mo	0.25	+	?				1.5	5.0		++				215/135	0	
	14	57	M	8 mo	0.7	10	17	20	15	38	1,800	143	123	3.3	57			105/60	0	
Group B	1	28	F	7 mo	0.1					+	2	8		0.1				104/72	+	
	2	19	F	8 mo	0.2					+	21	3		0.1	21			100/60	0	
	3	56	M	1 mo	0.3						10	16		2.14	178 to 53			115/80	0	
	4	49	F	36 mo +	0						10	3		0.2				122/80	0	
Group C	1	52	M	40 mo	0						0	0		0	22	6.4		115/85	+	
	2	43	M	36 mo	0						0	0							0	
	3	23	F	11 mo +	0							2	0	0				110/75	+	

\* The cases have been divided into three groups on the basis of urinary sediment A, "typical", B, nondescript, and C, normal

Clinical and Pathologic Data

Necropsy				
Glomeruli	Tubules	Blood Vessels (Arterioles)	Libman Sacks Endocarditis	Comment
None normal, "wire loop" lesions present, fibrosis, some crescents	Fatty degeneration	Many arterioles with thick hyalinized walls, partial occlusion		Clinically periarteritis nodosa, only case in series in which classic "wire loop" lesions present
Proliferation of Bowman's capsule, no crescents, thick individual loops	Normal	Some arterioles with marked medial necrosis and perivascular white blood cell collars	Nodules on tricuspid valve, ? atypical	Periarteritis nodosa with renal lesions resembling, but not typical of, those of glomerulonephritis, urine of assistance in diagnosis
Fibrosis and increased cellularity of loops, some fibrin plugs in capillaries	Slight fatty degeneration	Normal		Death due to pneumococcal sepsis, a case of severe lupus erythematosus disseminata
Some fibrosis and hyalinization, few crescents	Marked fatty degeneration	Only slight arteriolar thickening	Definite endocarditis with lesions on tricuspid and on mitral valve	Classic lupus erythematosus disseminata with Libman Sacks endocarditis, no pericarditis, hypertension, heart failure, uremia terminally
				Peculiar pneumonitis revealed by roentgen examination, pulmonary and renal discases predominant, no autopsy, renal lesions of aid in diagnosis
				Renal lesion the initial manifestation, followed by evidence of involvement of other organs in disseminated lupus erythematosus, one of Addis' cases in which the initial diagnosis in 1931 was glomerulonephritis
None normal, fibrosis, necrosis of media of arterioles	Fatty degeneration	Infiltration of adventitia with white cells, medial necrosis and thrombosis	Valve edges and chordae tendineae thickened?	Periarteritis nodosa with renal lesion, asthma was initial difficulty
Edematous	Edematous, fatty degeneration			Lupus erythematosus disseminata with renal lesions, diagnosis was glomerulonephritis in 1930, case discovered in review of Addis' files
"Nephritis"				Autopsy elsewhere, unable to get complete examination to report
				Muscle biopsy, subacute periarteritis myositis, urine of aid in diagnosis
				July 7, 1940, patient ill, pale, edematous, heart enlarged
				Sept 10, 1940 patient improved, peripheral neuritis, biopsy of muscle periarteritis nodosa
				Nov 14, 1940 patient improved
				March 13, 1941 patient improved, in August 1941 only trace of protein in urine
				Muscle biopsy periarteritis nodosa
Fibrosis and hyalinization	Fatty degeneration	Arterioles with hyalinized thick walls to point of occlusion		Periarteritis nodosa proved
None intact, many hyalinized, many crescents	Fatty degeneration	Arteriolar walls thick		Diagnosis of subacute glomerulonephritis at autopsy, clinically a clearcut case of periarteritis nodosa
				Classic lupus erythematosus disseminata with cardiac murmur of possible valvular lesion
Normal	Normal	Normal		Periarteritis nodosa with lesions of heart and lung, pneumonia peculiar to periarteritis
Thick basement membrane of capillary loop, some hyalinized glomeruli	Fatty degeneration	Not remarkable		Arterioles of heart, renal pelvis and other tissues infiltrated and surrounded by eosinophils
				Diagnosis unconfirmed, clinically a case of visceral angitis
Normal	Normal	Normal	Valvulitis with verrucae on chordae tendineae	Clinically disseminated lupus erythematosus, but at autopsy extensive periarteritis encountered a case which constitutes evidence in favor of considering these diseases as common entities
				Muscle biopsy periarteritis nodosa
				Clinically visceral angitis muscle biopsy normal vessels, subacute myositis



are reflected in the urinary sediment. Similar variations were observed in case 12, group A.

Another point of interest is that not only the urinary sediment but at times the clinical picture showed simultaneously the features of early and late stages of glomerulonephritis. It was common, for example, to see a patient with hypoproteinemic edema (degenerative stage) and retention of urea and hypertension (terminal stage). In this series normal blood pressures were encountered not only in those cases in which the kidneys were not affected but also in 8 cases in which there were severe renal lesions (group A, cases 2, 5, 6, 7, 8, 10, 12 and 14), in some of which there were gross signs of renal failure. Normal blood pressures were also encountered in the cases of visceral angitis during a stage of severe tubular degeneration, just as in the case of the "nephrotic" stage of ordinary nephritis. Hypertension, when it did occur, was with 1 exception always associated with renal failure.

Finally, there has been much speculation as to the relation of the various clinical syndromes which I have enumerated under the heading visceral angitis.<sup>6</sup> On the other hand, I do not advance the similarity of the urinary sediments in these clinical states as a basis for the view that they are all variants of one disease entity. I cannot do that, because it is known that in diseases of entirely diverse causation and pathogenesis one may in the end find sediments that are indistinguishable.

When a renal lesion exists in visceral angitis, it is of such a nature as to induce glomerular bleeding and the passage of fibrinogen through the glomerular membrane, with the formation of blood casts, fatty degeneration of tubule cells and local oliguria that leads to the formation of broad casts. There is thus a relation between the diseases grouped under this term, though it is not maintained that the renal lesions are histologically identical, still less that they have the same causation or pathogenesis. In case 1, group C, especially interesting in this connection, the patient showed the clinical features of lupus erythematosus, but at autopsy the classic lesions of periarteritis nodosa were revealed. In case 1, group A, also to the point, the clinical diagnosis was periarteritis, but at autopsy the "wire loop" glomerular lesions described in association with lupus erythematosus were found.

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6 (a) Keil, H. Dermatomyositis and Systemic Lupus Erythematosus. II. Comparative Study of Essential Clinicopathologic Features, *Arch Int Med* **66** 339 (Aug.) 1940. (b) Banks, B. M. Is There a Common Denominator in Scleroderma, Dermatomyositis, Disseminated Lupus Erythematosus, the Libman-Sacks Syndrome and Polyarteritis Nodosa? *New England J Med* **225** 433, 1941. (c) Denzer, B. S., and Blumenthal, S. Acute Lupus Erythematosus Disseminatus, *Am J Dis Child* **53** 525 (Feb.) 1937. (d) Ginzler and Fox.<sup>21</sup> (e) Rose and Pillsbury.<sup>22</sup>

## SUMMARY AND CONCLUSIONS

Twenty-one cases of periarteritis nodosa, lupus erythematosus disseminata, Libman-Sacks "disease" and the syndromes of Friedberg and Gross were studied with particular reference to the clinical manifestations of the renal lesion

In 7 cases no specific changes in urinary sediment were discovered, but in 14 cases a singular picture of the sediment was observed. The uniqueness of this picture lies in the presence of red blood cells, red cell casts, oval fat bodies, fatty casts, broad casts and abnormal quantities of protein in the same specimen of urine. These elements do not occur together in association with glomerulonephritis or with any other renal lesion with which I am familiar.

This unusual sediment is of diagnostic value in doubtful cases of the disorders just mentioned.

The term visceral angitis is advanced as a convenient clinical designation for these disorders and is not meant to imply a common etiologic relation.

Stanford University Hospitals

# EXCRETION OF COPROPORPHYRIN IN HEPATIC DISEASE

## III URINARY EXCRETION OF COPROPORPHYRIN IN HEPATIC INSUFFICIENCY DURING EPISODES CHARACTERIZED BY NEUROLOGIC MANIFESTATIONS

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NEW HAVEN, CONN

As stated in previous papers of this series,<sup>1</sup> it is probable that porphyrin arises within the body during the process of synthesis of hemoglobin, protoporphyrin III composing the prosthetic group of hemoglobin, myoglobin and various respiratory ferments,<sup>2</sup> and that porphyrin of isomeric series I, which arises as a useless by-product during this synthesis, as well as any porphyrin of isomeric series III that is not utilized, is excreted in the urine and feces as coproporphyrin. The total amount of coproporphyrin excreted as well as the ratio of urinary to fecal excretion depends chiefly on the rate of production of porphyrin and the efficiency of the liver, which is the more important organ of excretion of porphyrin, the kidneys normally excreting but

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Abstract of a portion of thesis submitted to the Faculty of the Graduate School of the University of Minnesota in partial fulfilment of the requirements for the degree of Ph D in Medicine

1 Nesbitt, S, and Snell, A M (a) The Excretion of Coproporphyrin in Hepatic Disease I Correlation of Urinary and Fecal Excretion with Parenchymatous Hepatic Damage, *Arch Int Med* **69** 573-581 (April) 1942, (b) Excretion of Coproporphyrin in Hepatic Disease II Urinary and Fecal Excretion in Biliary Obstruction, *ibid* **69** 582-588 (April) 1942

2 (a) Dobriner, K Porphyrin Excretion in Feces in Normal and Pathological Conditions, *J Biol Chem* **120** 115-127 (Aug) 1937 (b) Dobriner, K, and Rhoads, C P The Metabolism of Blood Pigments in Pernicious Anemia, *J Clin Investigation* **17** 95-103 (Jan) 1938 (c) Dobriner, K, Strain, W H, Localio, S A, Keutmann, H, and Stephens, D I II Coproporphyrin I Metabolism and Hematopoietic Activity, *Proc Soc Exper Biol & Med* **36** 755-756 (June) 1937 (d) Rimington, C Porphyrins and Their Relation to the Metabolism of Blood Pigments, *Proc Roy Soc Med* **32** 1268-1275 (Aug) 1939 (e) Lemberg, R Transformation of Haemins into Bile Pigments, *Biochem J* **29** 1322-1336 (June) 1935

a small fraction of the total porphyrin excreted<sup>3</sup> It has been demonstrated that in the event of parenchymatous hepatic damage the ratio of urinary excretion to fecal excretion is increased roughly in proportion to the degree of hepatic dysfunction<sup>1a</sup> and that in obstruction of the biliary ducts this ratio is also increased in proportion to the degree of obstruction When the continuity of the biliary passage is restored by operative means the normal ratio of urinary excretion to fecal excretion of coproporphyrin is restored, provided, of course, that the hepatic function is adequate<sup>1b</sup>

Four patients who had severe alcoholic cirrhosis of the liver afforded an opportunity for study of the daily urinary excretion of coproporphyrin during repeated episodes of acute hepatic insufficiency which were evidenced by periods of neurologic manifestations ranging from mild disorientation and psychotic behavior to deep coma Sometimes during such episodes choreiform movements occurred, and occasionally pathologic neurologic signs could be elicited, including a Babinski reflex and sustained ankle clonus At such times there was a decline in urinary output, the patient might become cyanotic and a peculiar odor, which has been described as "mousy," might be noticed During these periods the concentration of sugar and of electrolytes in the blood remained within normal limits The records of these patients have been reviewed in detail by Snell and Butt<sup>4</sup>

The patients were maintained on a meat-free diet throughout the period of study On the basis of Mann and Bollman's<sup>5</sup> studies they were placed on a high carbohydrate, high nonmeat protein, low fat diet to which were added vitamin supplements<sup>4</sup> In view of the interesting studies by Jolliffe and others,<sup>6</sup> intensive parenteral administration of vitamins was employed during the acute episodes The vitamins administered included at least 100 mg of nicotinic acid, 100 mg of

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3 Dobriner, K, and Rhoads, C P The Quantitative Determination of Urinary Coproporphyrin, *New England J Med* **219** 1027-1029 (Dec 29) 1938  
 Watson, C J Concerning the Naturally Occurring Porphyrins I The Isolation of Coproporphyrin I from the Urine in a Case of Cinchophen Cirrhosis, *J Clin Investigation* **14** 106-109 (Jan) 1935, Concerning the Naturally Occurring Porphyrins IV The Urinary Porphyrin in Lead Poisoning as Contrasted with That Excreted Normally and in Other Diseases, *ibid* **15** 327-334 (May) 1936  
 Dobriner<sup>2a</sup>

4 Snell, A M, and Butt, H R Hepatic Coma Observations Bearing on Its Nature and Treatment, *Tr A Am Physicians* **56** 321-329, 1941

5 Mann, F C, and Bollman, J L Jaundice A Review of Some Experimental Investigations, *J A M A* **104** 371-374 (Feb 2) 1935

6 Jolliffe, N, Bowman, K M, Rosenblum, L A, and Fern, H D Nicotinic Acid Deficiency in Encephalopathy, *J A M A* **114** 307-312 (Jan 27) 1940  
 Jolliffe, N Effects of Vitamin Deficiency on Mental and Emotional Processes, *A Research Nerv & Ment Dis, Proc* (1938) **19** 144-153, 1939

thiamine chloride, 200 mg of ascorbic acid and one of the preparations which possess vitamin K activity<sup>4</sup> It is interesting that the patients did recover repeatedly from the acute episodes

One of the patients was confused and disoriented when he entered the hospital, and he soon lapsed into deep coma, from which he roused During a comparatively brief stay in the hospital he experienced one other period during which he was stuporous and semicomatose Again he improved, and he left the hospital Three of the patients were observed over long periods during which they experienced repeated episodes of acute hepatic insufficiency, in which the state ranged from confusion to deep coma Two of the patients exhibited a Babinski reflex and sustained ankle clonus during some episodes One patient suffered

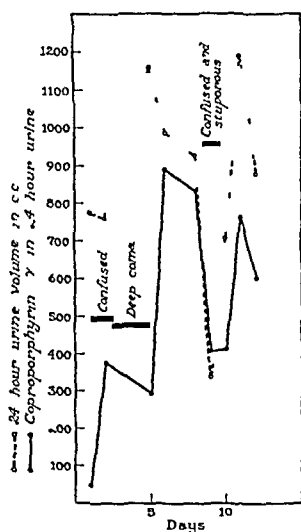


Chart 1 (case 1) —Excretion of urinary coproporphyrin

a terminal hemorrhage from a ruptured varix One patient died, mesenteric thrombosis having developed One patient returned to his home and has continued to improve

In each instance daily determinations of the urinary coproporphyrin excreted were made, and these are represented graphically in charts 1 to 4 along with the corresponding volumes of urine The periods of acute hepatic insufficiency have been indicated From this study several things became apparent It was noted that the amount of coproporphyrin excreted in the urine was surprisingly parallel to the corresponding volume of urine It was observed also that before and during each episode of acute hepatic insufficiency a sharp decline in the amount of urinary coproporphyrin as well as in the volume of urine occurred and that the values increased abruptly as the patient emerged from the acute episode

The first patient (chart 1) on admission was disoriented, and he soon lapsed into deep coma. During this episode the amount of urinary coproporphyrin, although greater than the normal range of 0 to 100 gammas, was relatively low compared with the values for urinary coproporphyrin between the acute episodes. As the patient improved clinically, the value rose sharply. On the eighth day he experienced another such episode—he became confused and stuporous, and the volume of the urine and the urinary excretion of coproporphyrin again were diminished. The values again increased abruptly as he improved.

The second patient (chart 2) experienced five such episodes of acute hepatic insufficiency, and the same findings with regard to urinary volume and urinary coproporphyrin were noted. In this instance, on several occasions (as indicated by *a*) after the final episode of acute hepatic insufficiency a relatively low value

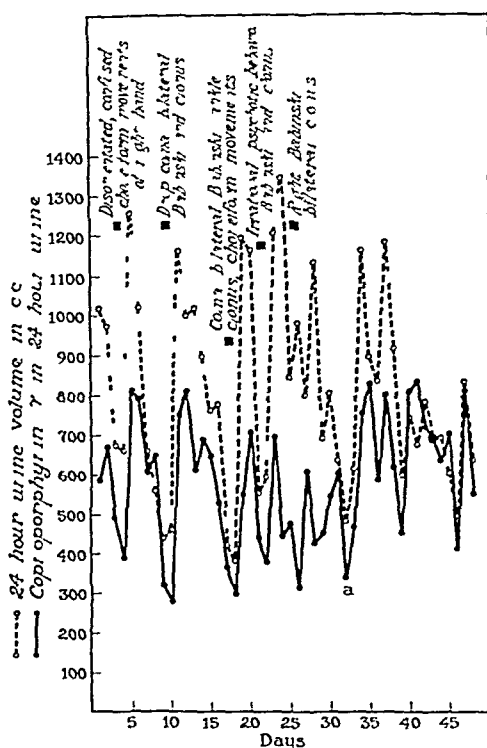


Chart 2 (case 2) —Excretion of urinary coproporphyrin

for both urinary volume and excretion of coproporphyrin was observed, at these times the patient did not exhibit any untoward neurologic manifestations.

The third patient (chart 3) experienced eight episodes of acute hepatic insufficiency over a period of three months, with the usual changes in urinary volume and excretion of coproporphyrin. Similar low values were observed in several instances (indicated by *a* to *e*) without any clinical evidence of acute hepatic insufficiency.

The course of the fourth patient (chart 4), who was observed over a period of three months, was similar to that of the third patient. Eight episodes of acute hepatic insufficiency occurred, with the usual findings as to values for urinary volume and for urinary excretion of coproporphyrin. Again on several occasions (indicated by *a* to *e*) low values were observed in the absence of clinical evidence for acute hepatic insufficiency.

It has long been recognized that a diminished urinary output occurs before and during episodes of acute hepatic insufficiency and that there is an elevation of the nonprotein nitrogen content of the blood at such

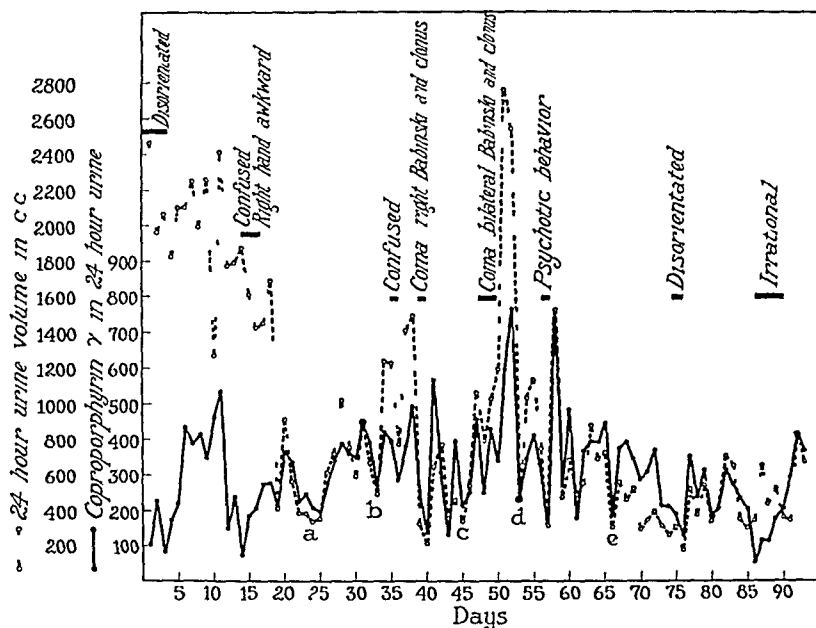


Chart 3 (case 3) — Excretion of urinary coproporphyrin

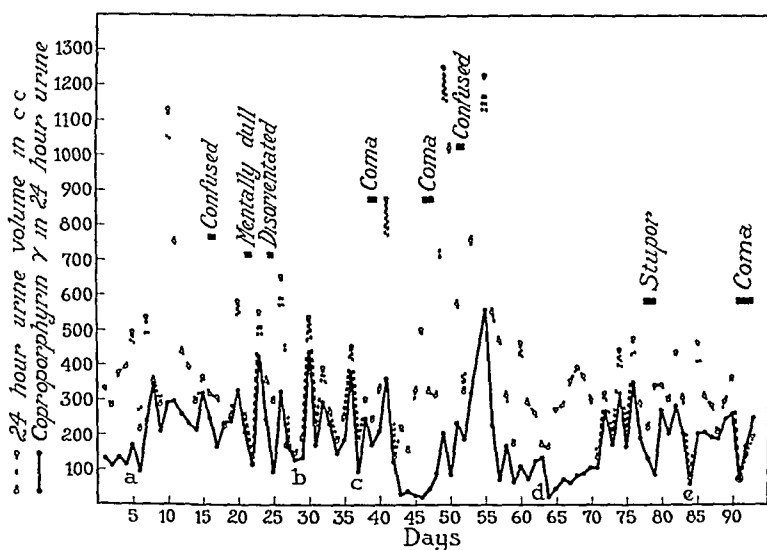


Chart 4 (case 4) — Excretion of urinary coproporphyrin

times. Many workers have attributed these changes to failing renal function in addition to hepatic insufficiency, the acute picture thus being produced by the retention of hypothetical toxic substances. It is interesting to speculate as to what, if any, part retention of porphyrin may have to play in relation to these toxic substances

30336.

## SUMMARY AND CONCLUSIONS

In 4 cases of severe alcoholic cirrhosis of the liver it has been demonstrated that a close correlation exists between the values for urinary coproporphyrin excreted daily and for the corresponding urinary volume and that these values bear a definite relation to the onset and the course of periods of acute hepatic insufficiency. It seems fair to assume that the declining urinary excretion of coproporphyrin observed with the fall of urinary output before and during such periods is merely a reflection of a diminished renal function which occurs together with the diminished hepatic function at such times.

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# ALKAPTONURIA WITH HYPERURICEMIA

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Alkaptonuria is an unusual disease, but the metabolic disorder which it represents assumes considerable importance because of the light it sheds on the normal catabolism of two essential amino acids. The existence of the disease has apparently been known since the sixteenth century,<sup>1</sup> but only with the more recent knowledge of amino acid metabolism has its true nature been understood. It may be regarded as a deficiency disease, the deficiency probably being intrinsic rather than extrinsic. Although the deficient factor is not known, it is presumably a catalyst for a specific stage in the breakdown of tyrosine and phenylalanine. This will be considered later and in greater detail.

The clinical detection of alkaptonuria is usually simple. The most common history obtained is that of a peculiar blackening or darkening of an infant's urine-moistened diaper when it is exposed to air. Sometimes the urine is abnormally dark when voided. Occasionally, the condition is not noticed until later life, when a reducing substance which proves not to be sugar is detected by routine urinalysis. However, in this event the probability is that the condition has existed since birth. Several members of a family are commonly affected, instances of the disease among ancestors may be recalled. It is not apparent whether the disease tends more toward maternal or paternal transmission. No other symptoms are observed in alkaptonuria until relatively late in the course of the disease when ochronosis appears. This was first described by Virchow,<sup>2</sup> who did not associate it with alkaptonuria. Ochronosis is characterized by a bluish discoloration of the cartilages, most easily discernible in the ears and the alae nasi, and is due to the deposition of oxidation products of homogentisic acid. Albrecht<sup>3</sup> expressed the belief that this pigment resulted from the combination of homogentisic acid or one of its derivatives with chondromucin or chondroitin-sulfuric acid in the cartilages. Although there is a predilection for the cartilages, the abnormal pigmentation is occasionally visible in the skin and the nails and in pingueculae. A similar picture

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From the medical service of Dr. George Baehr and the laboratories of the Mount Sinai Hospital.

1 Garrod, A. E. *Inborn Errors of Metabolism*, ed. 2, London, Oxford University Press, 1923.

2 Virchow, R. *Ein Fall von allgemeiner Ochronose der Knorpel und knorpelartiger Theile*, *Virchows Arch. f. path. Anat.* **37**: 212, 1866.

3 Albrecht, H. *Ueber Ochronose*, *Ztschr. f. Heilk.* **23**: 366, 1902.

may be seen in chronic poisoning with phenol. Degenerative changes take place in the articular cartilages, with the production of a particularly disabling form of osteoarthritis. Erosion of the intervertebral disks causes osteitis deformans alkaptonuria, as described by Soderbergh<sup>4</sup> and noted by Osler<sup>5</sup> and Albiecht.<sup>3</sup> This presents the clinical picture of spondylitis but is characterized by the absence of vertebral bridging in roentgenograms. Ochronosis does not develop in all cases of alkaptonuria, but the incidence has been high enough to account for the varied therapeutic efforts, which, unfortunately, have met with little success to date. A false positive Wassermann reaction is not uncommonly associated with alkaptonuria. Soderbergh<sup>6</sup> reported a case in which the Wassermann reaction, which became negative after a course of therapy with mercury inunctions, again was positive after the patient ingested excess tyrosine. Syphilis was most unlikely in this case. Soderbergh called attention to the similarity of the bone changes to those occurring in Paget's disease, in which condition also the Wassermann reaction is occasionally positive.

In an excellent review Garrod<sup>1</sup> cited 3 of the earliest cases on record. In 1584 Scribonius told of a perfectly healthy schoolboy whose urine was black. In 1609 Schenck described the case of a monk with black urine, and in 1649 Zacutus Lusitanus wrote of black urine in a boy whose urine was unaffected by drastic measures but who achieved healthy manhood, black urine and treatment notwithstanding. In 1859 Bodeker<sup>7</sup> isolated from the urine of a patient with glycosuria a second reducing substance, which turned black on the addition of alkali. This he named "Alkapton." In 1861<sup>8</sup> he first described and named the disease alkaptonuria. In 1886 Brune<sup>9</sup> reported the first case in America.

Bateson,<sup>10</sup> Punnett<sup>11</sup> and Garrod<sup>12</sup> presented evidence that alkaptonuria is a rare mendelian recessive character. In most of the cases described the condition was shown to be hereditary. Wolkow and

4 Soderbergh, G. Ueber Ostitis deformans ochronotica, *Neurol Centralbl* **21**, 1362, 1913.

5 Osler, W. The Pigmentation of Cartilages, Sclerotics, and Skin in Alkaptonuria, *Lancet* **1**:10, 1904.

6 Soderbergh, G. Zur Klinik der Alkaptonurie, *Nord med ark*, 1915, vol 48, no 3 and no 4.

7 Bodeker, C. Ueber das Alcapton, *Ztschr f rat Med* **7**:130, 1859.

8 Bodeker, C. Das Alkapton, *Ann d Chem u Pharmacol* **117** 98, 1861.

9 Brune, T. B. A Reducing Substance in Urine, Resembling Glucose, *Boston M & S J* **115** 621, 1886.

10 Bateson, W., in Report of the Evaluation Committee of the Royal Society, London, 1902, no 1, p 133, note.

11 Punnett, R. C. Mendelism in Relation to Disease, *Proc Roy Soc Med (Epidemiol Sect)* **1** 135, 1908.

12 Garrod, A. E. Inborn Factors in Disease, New York, Oxford University Press, 1931.

Baumann<sup>13</sup> in 1891 identified the substance known as "alkapton" as homogentisic acid. In 1895 Baumann and Frankel<sup>14</sup> were able to synthesize homogentisic acid and prove its formula. This work was corroborated later by Osborne<sup>15</sup> and Neubauer and Flatow<sup>16</sup>.

Wolkow and Baumann<sup>13</sup> demonstrated increased excretion of homogentisic acid after the ingestion of tyrosine by a subject with alkaptonuria. Falta and Langstein<sup>17</sup> showed this phenomenon to occur after the ingestion of phenylalanine as well. Both of these amino acids contain the benzene ring, which human beings do not synthesize and which patients with alkaptonuria apparently cannot break down. Gibson and Howard<sup>18</sup> administered tyrosine and a measured diet to a patient with alkaptonuria and noted the characteristic rise in excretion of homogentisic acid. They concluded that the disease is due to the incomplete catabolism of the aromatic fraction of tyrosine and phenylalanine. Papageorge and Lewis<sup>19</sup> were able to produce excretion of homogentisic acid by white rats by daily oral administration of *l*-phenylalanine (0.3 Gm per hundred grams of body weight). Sealock and Silberstein<sup>20</sup> produced it by the administration of extra tyrosine to guinea pigs on diets deficient in vitamin C. The latter authors were able to repeat this experiment successfully on 2 normal human beings. However, as shown in a later report, Sealock and associates<sup>21</sup> were unable to affect the metabolism of homogentisic acid in a patient with alkaptonuria by the administration of ascorbic acid, although the urine no longer darkened on standing. Sealock and Silberstein suggested that vitamin C is the deficient factor in experimental alkaptonuria, while the missing factor in hereditary

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13 Wolkow, M., and Baumann, E. Ueber das Wesen der Alkaptonurie, *Ztschr f physiol Chem* **15** 228, 1891.

14 Baumann, E., and Frankel, S. Ueber die Synthese der Homogentisinsäure, *Ztschr f physiol Chem* **20** 219, 1895.

15 Osborne, W. A. A New Synthesis of Homogentisic Acid, *Proc Physiol Soc London*, 1903, p. xiii.

16 Neubauer, O., and Flatow, L. Synthesen von Alkaptonsäuren, *Ztschr f physiol Chem* **52** 375, 1907.

17 Falta, W., and Langstein, L. Die Entstehung von Homogentisinsäure aus Phenylalanin, *Ztschr f physiol Chem* **37** 513, 1903.

18 Gibson, R. B., and Howard, C. P. A Case of Alkaptonuria with a Study of Its Metabolism, *Arch Int Med* **28** 632 (Nov) 1921.

19 Papageorge, E. T., and Lewis, H. B. Comparative Studies of the Metabolism of the Amino Acids. VII. Experimental Alkaptonuria in the White Rat, *J Biol Chem* **123** 211, 1938.

20 Sealock, R. R., and Silberstein, H. E. The Control of Experimental Alkaptonuria by Means of Vitamin C, *Science* **90** 517, 1939.

21 Sealock, R. R., Galdston, M., and Steele, J. M. Administration of Ascorbic Acid to an Alkaptonuric Patient, *Proc Soc Exper Biol & Med* **44** 580, 1940.

alkaptonuria is as yet unknown Papageorge, Frohlich and Lewis<sup>22</sup> produced a great increase in the urinary excretion of homogentisic acid in patients with alkaptonuria by the oral administration of phenylalanine, in amounts roughly equal to 70 per cent of the total amount theoretically obtainable by the complete conversion of phenylalanine. They expressed the belief that homogentisic acid was an intermediate product of normal protein metabolism. Butts, Dunn and Hallman<sup>23</sup> produced alkaptonuria by feeding phenylalanine to normal rats but were unable to do so by feeding tyrosine.

Temporary disappearance of alkaptonuria during a period of starvation in which there was associated ketone acidosis was reported by Katsch,<sup>24</sup> and Reinwein<sup>25</sup> demonstrated a lowering of homogentisic acid excretion in a patient on a low carbohydrate diet. Diaz, Mendoza and Rodriguez<sup>26</sup> could not influence the excretion of homogentisic acid by the administration of a high ketone diet, which resulted in ketosis. Complete carbohydrate deprivation had no effect. Lieb and Lanyar<sup>27</sup> produced ketosis by the administration of a low carbohydrate diet but also were unable to corroborate the work of Reinwein. These authors<sup>28</sup> also tried reducing the protein intake of a patient with alkaptonuria. The ratio of homogentisic acid excretion to nitrogen excretion remained constant, despite diminution of the latter. Braid and Hickmans,<sup>29</sup> studying an infant with alkaptonuria, found that after a thirty hour period of starvation during illness homogentisic acid disappeared from the urine and was not replaced by acetone. A case of temporary alkaptonuria was reported by Furniss.<sup>30</sup> The alkaptonuria disappeared on recovery from an attack of jaundice and perhaps merely represented a temporary disturbance in tyrosine metabolism.

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22 Papageorge, E. T., Frohlich, M. M., and Lewis, H. B. Excretion of Homogentisic Acid After Oral Administration of Phenylalanine to Alcaptonuric Subjects, *Proc Soc Exper Biol & Med* **38**:742, 1938.

23 Butts, J. S., Dunn, M. S., and Hallman, L. F. Studies in Amino Acid Metabolism. IV. Metabolism of *dl*-, Phenylalanine and *dl*-Tyrosine in the White Rat, *J Biol Chem* **123**: 711, 1938.

24 Katsch, G. Alkapton und Aceton, *Deutsches Arch f klin Med* **127**: 210, 1918, **134**:59, 1920.

25 Reinwein, H. Untersuchungen uber die Alkaptonurie, *Deutsches Arch f. klin Med* **170**: 327, 1931.

26 Diaz, C. J., Mendoza, H. C., and Rodriguez, J. S. Alkapton, Aceton, und Kohlhydratmangel, *Klin Wchnschr* **18**: 965, 1939.

27 Lieb, H., and Lanyar, F. Alkaptonurie und Kohlhydratenziehung, *Ztschr. f physiol Chem* **186**: 119, 1929.

28 Lieb, H., and Lanyar, F. Alkaptonurie bei minimaler Eiweisszufuhr, *Ztschr f physiol Chem* **186**: 111, 1929.

29 Braid, F., and Hickmans, E. M. Metabolic Study on an Alkaptonuric Infant, *Arch Dis Childhood* **4**:389, 1929.

30 Furniss, H. D. Alkaptonuria, *J Mt Sinai Hosp* **4**: 720, 1938.

By the administration of thyroïd Schmieding<sup>31</sup> caused a parallel increase in nitrogen excretion and homogentisic acid excretion in a 7 year old girl with alkaptonuria. When there was evidence of thyrotoxicosis, the excretion of homogentisic acid exceeded that of nitrogen, with the restoration of the former relation after withdrawal of the thyroïd. This author expressed the belief that there was a congenital defect of an enzyme, perhaps of hepatic origin. Klein and Bloch<sup>32</sup> reported a possible temporary improvement in a patient with alkaptonuria after the injection of liver extract, with subsequent complete relapse. Diaz, Mendoza and Rodriguez<sup>26</sup> could not demonstrate any effect of liver extract in a patient with the disease nor could Mosonyi<sup>33</sup>. In the report of Mosonyi and of Diaz and associates favorable results from the use of ascorbic acid were described. Mosonyi reported relief of arthralgias, which recurred when the administration of ascorbic acid was stopped and liver extract was given and which were again relieved by the administration of ascorbic acid (150 mg per day), with which was given adrenal cortex extract. Sealock, Galdston and Steele<sup>21</sup> were unable to demonstrate any effect from the administration of ascorbic acid up to 4 Gm per day. Diaz and associates<sup>26</sup> suggested that ascorbic acid merely prevented the oxidation of alkapton in the urine, consequently avoiding blackening of the urine, with little true metabolic effect.

#### REPORT OF A CASE

P. H., an American-born white housewife aged 24, came to the outpatient department in February 1936, complaining of pain in the right sternoclavicular joint. She also stated that her under garments became blackened by her urine, of which she had been slightly incontinent since the delivery of her second child. The discoloration was not immediate, since the urine was light in color when voided. This urinary abnormality had been observed in the patient by her mother, who had noticed a blackening of her diapers after birth. There were no siblings. There was no familial history of any similar disturbance, the patient's mother being alive and having diabetes and her father having died of an abdominal neoplasm at the age of 44. The patient's 2 children had never had any urinary abnormalities or any other significant deviation from normal. The patient's past history was essentially irrelevant. She used no alcohol, tobacco or drugs.

*Physical Examination*—The patient's general appearance was one of good health. She was moderately obese. The hair was of normal texture, and there were no signs of myxedema. There were numerous dental cavities. The thyroid was not enlarged. The heart and the lungs were normal to percussion and auscultation. The blood pressure was 110 systolic and 80 diastolic. There was a small umbilical hernia. There was no neurologic abnormality or any evidence of pig-

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31 Schmieding, E. Stoffwechseluntersuchungen bei kindlicher Alkaptonurie, *Monatschr f Kinderh* **73** 216, 1938.

32 Klein, O., and Bloch, K. Beseitigung der Alkaptonurie durch parenterale Zufuhr von Leberextrakten, *Klin Wchnschr* **15** 1684, 1936.

33 Mosonyi, L. A propos de l'alkaptonurie, *Presse med* **47** 708, 1939.

mentation in the aural and nasal cartilages. There was a small cystocele, with incontinence after straining. The right sternoclavicular joint was red, swollen and tender, and there was limitation of abduction of the arm. A routine examination of the urine failed to reveal any abnormality. The Wassermann reaction of the blood was negative. Roentgen examination of the affected joint did not show any bony abnormality. A year later, after persistent joint pain, roentgen examination again failed to show any bony abnormality.

Despite careful dental attention there was no improvement. In 1937 a course of therapy with a preparation containing organic iodine and casein (activin) was ineffective. In 1939 more thoroughgoing laboratory studies were performed.

The urine was reported to contain alkapton bodies. The hemoglobin concentration was 77 per cent (Sahli). The white cell count was 6,500, with 59 per cent polymorphonuclear leukocytes (all segmented), 37 per cent lymphocytes, 2 per cent mononuclear leukocytes and 2 per cent eosinophils. There was some basophilic stippling of the red corpuscles. The erythrocyte sedimentation time was normal. Per hundred cubic centimeters the blood contained 12 mg of urea nitrogen, 95 mg of sugar, 210 mg of cholesterol, 115 mg of esterified cholesterol, 96 mg of

*Effect of the Administration of Ascorbic Acid on the Urinary Excretion of Homogentisic Acid by a Patient with Alkaptonuria*

Date	Medication	Urine Excreted, Cc /24 Hr	Homogentisic Acid Excreted, Gm /24 Hr
3/10/40	None	2,600	9.62
3/17/40	300 mg of ascorbic acid daily for 3 preceding days	2,150	6.83
3/20/40	None	2,370	10.70
4/17/40	300 mg of ascorbic acid daily	2,100	6.91
4/22/40	300 mg of ascorbic acid daily	1,750	6.48
4/23/40	300 mg of ascorbic acid daily	1,900	6.46
6/19/40	None	1,700	9.14

calcium, 77 King-Armstrong units of phosphatase and 86 mg of uric acid. The urine of each of the patient's 2 children was found to be free of alkapton bodies. The urine of the patient's mother, who had diabetes, contained a reducing substance, which turned out to be sugar and not homogentisic acid.

*Course of Illness*—The patient began complaining of pain in the left sternoclavicular joint as well. Another roentgenogram, taken in September 1940, showed considerable formation of new bone above the right sternoclavicular joint, with the formation of a spur 3 cm from the proximal end of the clavicle. The articular margin of the sternum was irregular and showed evidence of formation of new bone. The left sternoclavicular joint showed some evidence of osteoarthritis. The roentgenologist suggested that the changes on the right side were probably due to an osteoarthritic process.

On a second determination the blood level of uric acid was 7.9 mg per hundred cubic centimeters. After the administration of tincture of colchicum seed up to tolerance the blood level of uric acid rose to 13.3 mg per hundred cubic centimeters, probably because of mobilization, since it dropped back to 8.6 mg per hundred cubic centimeters with abatement of the effect of the colchicum seed. After exhibition of the drug there was marked amelioration of the arthritic symptoms.

*Metabolic Studies*—Because of the improvement after the administration of ascorbic acid reported by other authors it was decided to perform quantitative studies

of urinary excretion of homogentisic acid to determine any possible influence of vitamin C. The diet was not weighed but was kept approximately constant. The determinations of alkapton were made according to the silver reduction method of Baumann<sup>34</sup>. The accuracy of this method was supported by confirmatory results of determinations done according to the method of Lieb and Lanyar<sup>35</sup>. The results are summarized in the table.

While the patient was taking ascorbic acid, one determination of the total amount excreted in a single day yielded a value of 273 mg. The urine, which formerly darkened after standing several hours, did not become dark after standing seventy-two hours. However, the under garments continued to be blackened as before, when the patient was incontinent. The ingestion of ascorbic acid did not affect the blood level of uric acid, which was 7.9 mg per hundred cubic centimeters during the period of vitamin medication, nor did it affect the arthritic symptoms. The tincture of colchicum seed did not affect the excretion of homogentisic acid. A short trial of administration of vitamin E did not produce either clinical or laboratory improvement.

At present the patient is improved, probably because of the tincture of colchicum seed which she is continuing to take periodically. Ascorbic acid (150 mg per day) is also being taken in an attempt to avoid future ochronosis. The prescribed diet is low in purine.

#### COMMENT

Most of the clinical and experimental evidence at hand points to the existence of homogentisic acid as an intermediate product of normal protein metabolism. Gross<sup>36</sup> stated that normal serum destroys homogentisic acid, with the probable production of acetone. Thus, it is apparent why alkapton bodies cannot be recovered under ordinary circumstances. However, transient alkaptonuria has been noted in association with illness,<sup>37</sup> and established alkaptonuria has disappeared during periods of starvation<sup>38</sup>. Furthermore, alkaptonuria can be produced experimentally by feeding excessive amounts of phenylalanine.<sup>19</sup> One of Abderhalden's laboratory assistants excreted homogentisic acid for twenty-four hours after ingesting a large amount of tyrosine.

The diagram, adapted from Neubauer, illustrates the probable course of tyrosine catabolism.

Gross expressed the opinion that patients with alkaptonuria lack an enzyme which is responsible for the last step in the diagram. The breaking of the benzene ring is the essential characteristic of this transition. Administration of tryptophan does not alter the ratio of homogentisic

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34 Baumann, E. Ueber die Bestimmung der Homogentisinsäure in Alkaptonharn, *Ztschr f physiol Chem* **16** 268, 1892.

35 Lieb, H., and Lanyar, F. Ueber die jodometrische Bestimmung der Homogentisinsäure in Harn, *Ztschr f physiol Chem* **181** 199, 1929.

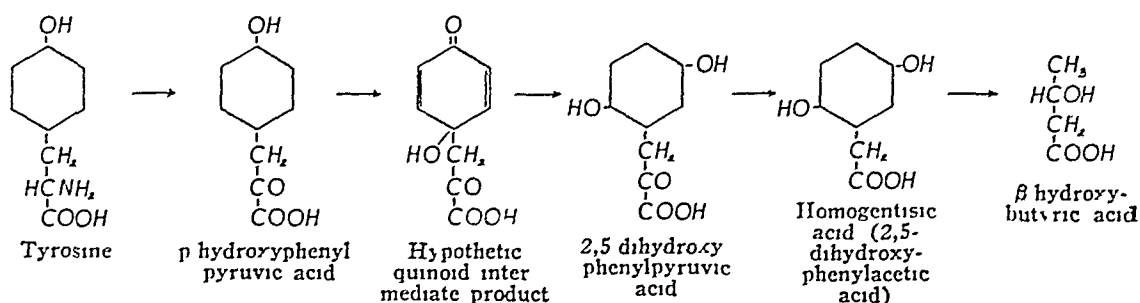
36 Gross, O. Ueber den Einfluss des Blutserums des Normalen und des Alkaptonurikers auf Homogentisinsäure, *Biochem Ztschr* **61** 165, 1914.

37 Garrod<sup>1</sup>. Furniss<sup>30</sup>

38 Katsch<sup>24</sup>. Braid and Hickmans<sup>29</sup>

acid excretion nitrogen excretion in patients with alkaptonuria. This fact seems to contravert Gross's contention, since this amino acid also contains a benzene ring. However, in this instance the benzene ring is part of the indole grouping, and its catabolism differs from that of tyrosine and of phenylalanine, which are the only parent substances of homogentisic acid.

It is true that the formulas shown represent merely a logical path of catabolism, without positive proof. The fact that even in patients with alkaptonuria the excretion of homogentisic acid is not quantitatively proportional to the ingested tyrosine or phenylalanine suggests a distorted, instead of an interrupted, catabolic pathway. However, this hypothesis does not consider the possibility of the utilization of these amino acids in protein synthesis or storage. The administration of ascorbic acid resulted in a decrease in alkapton excretion of roughly 30 per cent. Since the test employed was one involving silver reduction, the presence of vitamin C, a reducing agent, introduced an error, which,



The probable course of tyrosine catabolism (adapted from Neubauer)

if one considers the determination of ascorbic acid excretion, apparently did not exceed 5 per cent. It will be recalled that the darkening of the urine did not occur during the administration of ascorbic acid, although the under garments still were blackened. A similar observation was also made by Sealock and associates<sup>21</sup>. Although it appears that a true reduction in the excretion of homogentisic acid was effected, it is probable that the effect of vitamin C was merely secondary in the urine.

From the data presented, it is evident that although the administration of quantities of vitamin C well in excess of the estimated normal daily requirement appeared to lower the output of homogentisic acid, the fundamental distortion of metabolism was not affected. The apparent sparing action of vitamin C does not provide the answer to the question of the nature of the intrinsic deficiency. If it did, complete elimination of alkapton bodies from the urine would be expected.

It is tempting to speculate about a possible causative relation between the alkaptonuria and the hyperuricemia in the case presented. Because



of the favorable symptomatic response to tincture of colchicum seed, which was accompanied by alteration of the blood level of uric acid, it might be permissible to ascribe the hyperuricemia to the existence of true gout. But it is felt that there is insufficient evidence to justify such a claim. From what little is known of the two conditions, alkaptonuria and gout, there is some similarity of disease pattern. They are both apparently due to some specific intrinsic deficiency. There is abnormality of nitrogen metabolism in both, and in both there is destruction of cartilage and replacement by an abnormal metabolic deposit, severe joint manifestations occurring late in both diseases. However, beyond these superficial resemblances, the characteristics are divergent and need no elucidation here. If there were any significant causative relation, other cases of coexistent alkaptonuria and gout would surely have been described. A careful scrutiny of the literature failed to disclose a single additional case in which alkaptonuria and gout (or hyperuricemia) were coexistent. Ravold and Warren<sup>39</sup> reported a case in which they were able to demonstrate diminished urinary excretion of uric acid but gave no figures for blood levels of uric acid. They mentioned several authors who demonstrated apparent decreases in excretion of uric acid, as well as several who made no reference to such a decrease. No data on the blood were available to Ravold and Warren, and there were apparently no clinical manifestations to suggest gout. Adler<sup>40</sup> described a case in which excretion of uric acid remained constant during a rise in excretion of homogentisic acid. In the case described by Gibson and Howard<sup>18</sup> there was moderately high urinary excretion of uric acid, but no determination of the blood level of uric acid was made.

If there existed any fundamental relation between the alkaptonuria and the hyperuricemia in this case, any therapeutic attempt effective for one condition might have been expected to exert some effect on the other. This did not occur. Nevertheless, because it is reasonable to expect a common causation for the components of any syndrome, despite the lack of definite evidence for it in this case, the presence of two conditions reflecting distinct metabolic disorders in a single person may be more than an interesting coincidence.

#### SUMMARY

A case of alkaptonuria with hyperuricemia is presented. This is the first reported case in which these two conditions representing distinct metabolic disturbances have been coexistent. There was apparently no

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39 Ravold, A., and Warren, W. H. A Case of Alcaptonuria, *J Biol Chem* **7** 465, 1910

40 Adler, O. Ueber Alkaptonurie, *Biochem Ztschr* **21** 5, 1910

connection between the two disturbances, and laboratory studies and therapeutic efforts failed to reveal any

Reduction in excretion of homogentisic acid was noted after the administration of ascorbic acid. It is probable that this was a secondary effect, because (*a*) ascorbic acid merely by virtue of its reducing properties can prevent darkening of the urine and (*b*) complete absence of homogentisic acid from the urine was not achieved.

Administration of ascorbic acid did not affect the blood level of uric acid, nor did administration of tincture of colchicum seed affect the excretion of homogentisic acid.

The mechanism of alkaptonuria is discussed.

Dr. M. Volterra performed the determinations of homogentisic acid.

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# EFFECT OF MASSIVE DOSES OF VITAMIN D ON CALCIUM AND PHOSPHORUS METABOLISM

OBSERVATIONS ON PATIENTS WITH ATROPHIC SPONDYLITIS AND  
WITH DEGENERATIVE ARTHRITIS OF THE SPINE

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An adequate intake of vitamin D is essential for the optimal utilization of calcium and phosphorus in the normal metabolism of the human body. The minimal daily requirement is unknown, there being no conclusive experimental data on this subject. It is generally assumed that a daily intake of 300 to 600 U S P units of vitamin D is sufficient. This is supplied to healthy persons by a well balanced diet and exposure to sunlight. In persons with chronic arthritis there may be inadequacy in both these factors. This has been suggested by Irons,<sup>1</sup> who recommended that the deficiency be met by increasing the intake of vitamin D. Buckley<sup>2</sup> advocated the use of cod liver oil as part of the general treatment of arthritis.

In recent years vitamin D has been used extensively in amounts greater than its physiologic requirement in the treatment of arthritis. It was originally so used in massive doses by Dreyer and Reed.<sup>3</sup> Different investigators have reported their experience with this form of therapy, however, the results have not been uniform. Some patients showed definite improvement, while in others there was no appreciable change. It is difficult to evaluate reported therapeutic results in chronic arthritis as there is no uniform method of recording the clinical changes. Spontaneous remissions and seasonal variations are known to occur.

Reports in the literature show a wide variation in the laboratory findings following massive dose therapy with vitamin D. Dreyer and Reed<sup>3</sup> found the serum calcium elevated to as high as 30 mg per hun-

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1 Irons, E E. Chronic Arthritis. A General Disease Requiring Individualized Treatment, *Ann Int Med* **9** 1695 (June) 1936

2 Buckley, C W. Prognosis in Arthritis, *Lancet* **1** 1023 (May 2) 1936

3 Dreyer, I, and Reed, C I. Treatment of Arthritis with Massive Doses of Vitamin D, *Arch Phys Therapy* **16** 537 (Sept) 1935

dred cubic centimeters, while Wyatt and his associates<sup>4</sup> reported an increase of only 0.75 to 0.95 mg per hundred cubic centimeters. In many cases of atrophic arthritis there was a subsequent decrease in the sedimentation rate. Steck<sup>5</sup> reported that increased bone density was noted after the administration of vitamin D to patients with atrophic arthritis. No changes were observed by Vrtiak and Lang.<sup>6</sup> The last-named authors, moreover, noted signs of toxicity in all their patients receiving massive doses. In a large series of cases Steck and his associates<sup>7</sup> observed toxic effects in 8 per cent of their patients. Dreyer and Reed<sup>8</sup> failed to find any relation between high serum calcium and toxicity. No complete studies of calcium and phosphorus metabolism were included in the previous reports concerning the effects of high levels of vitamin D in patients with chronic arthritis.

There is extensive literature on the subject of vitamin D and its relation to calcium and phosphorus metabolism. Most studies were made on experimental animals, while data on normal human subjects are incomplete. Albright and Sulkowitsch<sup>8</sup> reported the effect of massive doses of vitamin D on calcium and phosphorus metabolism in 3 patients with hypoparathyroidism. They concluded that the main action of vitamin D is to increase the absorption of calcium from the intestinal tract, with resultant secondary changes in the phosphorus metabolism.

Minor changes encountered in the bones of patients with chronic arthritis have led different investigators to the conclusion that there may be a disturbance in calcium and phosphorus metabolism in this disease. There is no known dysfunction of the parathyroids associated with chronic arthritis. Ropes and associates<sup>9</sup> failed to find any primary disturbance in calcium and phosphorus metabolism in patients with degenerative and with atrophic arthritis.

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4 Wyatt, B. L., Hicks, R. A., and Thompson, H. E. Massive Doses of Vitamin D in the Treatment of Proliferative Arthritis, *Ann Int Med* **10** 534 (Oct) 1936.

5 Steck, I. E. Clinical Experience in the Treatment of Arthritis with Massive Doses of Vitamin D, *Illinois M J* **71** 243 (March) 1937.

6 Vrtiak, E. G., and Lang, R. S. Observations on the Treatment of Chronic Arthritis with Vitamin D, *J A M A* **106** 1162 (April 4) 1936.

7 Steck, I. E., Deutsch, H., Reed, C. I., and Struck, H. S. Further Studies on Intoxication with Vitamin D, *Ann Int Med* **10** 951 (Jan) 1937.

8 Albright, F., and Sulkowitsch, H. W. The Effect of Vitamin D on the Calcium and Phosphorus Metabolism. Studies on Four Patients, *J Clin Investigation* **17** 317 (May) 1938.

9 Ropes, M., Short, C. L., Rossmesl, E., and Bauer, W. Calcium and Phosphorus Metabolism in Rheumatoid and Degenerative Arthritis, *J Clin Investigation* **16** 675 (July) 1937.

An increased loss of calcium has been demonstrated in the majority of patients with hyperthyroidism<sup>10</sup> Basal metabolic rates were studied in a number of patients with chronic arthritis by Pemberton and Tompkins<sup>11</sup>, Cecil, Barr and DuBois<sup>12</sup>, Hench<sup>13</sup> and, more recently, Rawles and his associates<sup>14</sup> They reported the basal metabolic rate was within the limits of normal in the majority of the patients investigated The incidence of low basal metabolic rates was greater in patients with degenerative arthritis In patients with active atrophic arthritis there was a slight elevation of the basal metabolic rate

A number of selected patients have been treated with massive doses of vitamin D in our clinic, but uniform results have not been obtained By placing certain of these patients in the hospital under controlled management and studying their calcium and phosphorus metabolism, an attempt was made to determine certain of the actual metabolic changes produced by massive doses of vitamin D We were also interested in possible changes produced by such treatment in the function of the parathyroids and the thyroid

#### METHOD AND MATERIAL

The 4 patients selected for this investigation all had chronic arthritis of the spine Their ages varied from 28 to 71 years The 2 younger patients, E M and A G, had active atrophic spondylitis, while the 2 older ones, J C and M C, had degenerative arthritis of the spine The essential features of the histories, as well as the results of physical and laboratory examination, are summarized in the case reports The nature and the purpose of this investigation were explained to the patients, and all 4 cooperated well in the collection of specimens

The routine methods employed were used by Puppel and Curtis<sup>10a</sup> The calcium and the phosphorus intake was maintained at a relatively low level by eliminating foods with a high content of these elements, nevertheless, a palatable diet was provided, such as would be tolerated by the patients over the long periods of investigation The patients ate all their food, and there was no change in the individual diet during the thirty-six days of observation Distilled water was used and its daily intake maintained at a constant level Sedatives and analgesics were employed occasionally The drugs given did not contain calcium or phosphorus During the investigation the patients were up and about the ward

10 (a) Puppel, I D, and Curtis, G M Calcium and Iodine Metabolism in Thyroid Disease, *Arch Int Med* **58** 957 (Dec) 1936 (b) Puppel, I D, Klassen, K P, and Curtis, G M The Calcium Metabolism in Thyroid Disease, *West J Surg* **48** 374 (June) 1940

11 Pemberton R, and Tompkins E H Studies on Arthritis in the Army Based on Four Hundred Cases II Observations on the Basal Metabolism, *Arch Int Med* **25** 241 (April) 1920

12 Cecil, R L, Barr, D P, and DuBois, E F Clinical Calorimetry XXXI Observations on the Metabolism of Arthritis, *Arch Int Med* **29** 583 (April) 1935

13 Hench, P S Systemic Nature of Chronic Infectious Arthritis, *Atlantic M J* **28** 425 (April) 1935

14 Rawles, W B, Reese, A A, Gruskin, B, and Gordon, A S Thyroid Activity in Chronic Arthritis, *Ann Int Med* **11** 1401 (Feb) 1938

The investigation of each of the 4 patients was maintained for thirty-six days. This was subdivided into three main divisions, each of four three day periods. The control period constituted twelve days. This was followed by twelve days during which the patients were given a high vitamin D intake. The preparation used in these studies was an activated ergosterol<sup>15</sup> assayed to contain 50,000 U S P units of vitamin D per capsule. The initial daily dose of 200,000 units was increased to 400,000 during the second three day period, then to 600,000 and 1,000,000 units daily, during the third and the last three day period, respectively. No vitamin D was given during the last twelve days of investigation.

The basal metabolic rate was determined on the morning of the first day of each period. A specimen of blood was drawn the same morning while the subject was fasting and analyzed within a few hours. The serum calcium was determined by the Clark and Collip<sup>16</sup> method and the inorganic phosphorus and the serum phosphatase by the methods of King<sup>17</sup>. The total calcium content of the food, feces and urine was determined by the method of Puppel and Curtis,<sup>10a</sup> while the total phosphorus content was determined by a modification of the King<sup>17a</sup> method. All specimens were analyzed in duplicate, and analyses were repeated when adequate checks were not obtained.

**CASE 1—History**—M C, a 57 year old white housewife, was admitted to the hospital on Dec. 28, 1937. Approximately eight years prior to admission severe pain had developed in her hands and feet. This was followed by pain in her back and shoulders. Her discomfort was relieved by salicylates. In 1935 she had had an attack of acute pain in the upper right quadrant of the abdomen, not associated with jaundice. This condition was given the diagnosis of acute cholecystitis. She had had an appendectomy at the age of 25 and a hysterectomy at 35.

**Physical Examination**—The patient was pale and somewhat emaciated. There was limitation of motion in the entire spine, particularly in the cervical portion. The spinal muscles were spastic and hypertrophied. The reflexes were normal.

**Laboratory Examination**—The hemoglobin content was 13.6 Gm per hundred cubic centimeters, with a red cell count of 4,820,000. The sedimentation rate was 0.3 mm per minute. The total white cell count was 4,000, with a normal differential count. The blood level of urea nitrogen was 14 mg per hundred cubic centimeters. There was a trace of albumin in the urine. The Wassermann reaction and the Kahn reaction were negative. The icteric index was 6. An intravenous

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15 The preparation employed was ergosterol activated by the Whittier method (electrical activation of heat-vaporized ergosterol). This preparation (ertron, supplied for this investigation by the Nutrition Research Laboratories, Inc., Chicago) has not been accepted by the Council on Pharmacy and Chemistry of the American Medical Association. There have been published claims that it is less toxic in equivalent doses than are other preparations of activated ergosterol. These claims have, however, been questioned (Freyberg, R. H. Treatment of Arthritis with Vitamin and Endocrine Preparations, *J A M A* **119** 1165 [Aug 8] 1942; Freeman, S. Irradiated Ergosterol Poisoning, Correspondence, *ibid* **119** 968 [July 18] 1942).

16 Clark, E. P., and Collip, J. B. A Study of the Tisdall Method for the Determination of Blood Serum Calcium with a Suggested Modification, *J Biol Chem* **63** 461 (March) 1925.

17 (a) King, E. J. The Colorimetric Determination of Phosphorus, *Biochem J* **26** 292, 1932. (b) King, E. J., Haslewood, G. A. D., and Delory, G. E. Micro-Chemical Methods of Blood Analysis, *Lancet* **1** 886 (April 10) 1937.

cholecystogram showed a normal gallbladder. Roentgen examination revealed lipping of the vertebral bodies of the entire spine, most marked in the dorsal portion. The intervertebral spaces were narrowed, and the vertebral bodies showed rarefaction. The apophyseal joints were normal. There was extensive calcification of the abdominal aorta.

*Diagnosis*—The diagnosis was degenerative arthritis of the spine.

*Course of Illness During Hospitalization*—This patient did not show any improvement while in the hospital. Salicylates and codeine were given for the relief of pain. No changes were noted in the blood, and the blood level of urea nitrogen was 15 mg per hundred cubic centimeters at the time of discharge from the hospital. Roentgenograms taken five months later were not appreciably different from the initial ones.

*CASE 2—History*—E. M., a 28 year old white farmer, was admitted to the hospital on March 1, 1938. At the age of 18 he had experienced pain and swelling in his ankles. This lasted about a year and was followed by involvement of both knees. At the age of 20 he had become aware of pain and stiffness in both hips and in the lower portion of his back. The stiffness progressed, and gradually over a period of six years the entire spine had become involved. Marked forward bowing occurred and was associated with sharp radiating pain in his back. The limitation of motion in his hips also progressed, and during the two years before admission both shoulders had become involved. There was no history of severe illness. The patient stated he had never had a syphilitic or a gonorrheal infection. He had had a partial thyroidectomy for nontoxic nodular goiter at the age of 25.

*Physical Examination*—The patient was pale and emaciated and walked with a waddling gait. Chest expansion was limited, and breathing was diaphragmatic. There was a systolic murmur. The heart was normal in size. The patient had moderate kyphosis, with complete fusion of the spine up to the middorsal region and little motion in the upper dorsal and the cervical portion of the spine. The motion in both shoulders and hips was greatly reduced in all directions, and there was pain on forced motion. The reflexes were normal.

*Laboratory Examination*—The hemoglobin content was 140 Gm per hundred cubic centimeters, with a red cell count of 4,450,000. The sedimentation rate was 14 mm per minute. The white cell count was 8,000, with an essentially normal differential count. The blood level of urea nitrogen was 150 mg per hundred cubic centimeters. The Wassermann reaction and the Kahn reaction were negative. The urine was normal. Roentgenograms showed extensive calcification of the anterior and the lateral ligaments of the vertebral bodies and moderate kyphosis of the spine, without narrowing of the intervertebral spaces. The apophyseal and the sacroiliac joints were completely obliterated. The articulation of the os pubis at the symphysis was completely calcified. The articular spaces of the hip joints were normal, with lipping of the rim of the acetabulum. There was obliteration of the costovertebral joints.

*Diagnosis*—The diagnosis was atrophic spondylitis.

*Course of Illness During Hospitalization*—During the administration of vitamin D the patient's appetite increased and he had less pain. There ensued 10 per cent more motion in his hips, with some resultant improvement in his gait. On April 16 the sedimentation rate of the blood had decreased to 0.6 mm per minute. No other changes in the blood were noted.

**CASE 3—History**—J C, a 71 year old white retired salesman, was admitted to the hospital on March 4, 1938. When he was 69, radiating pain had developed in his right shoulder and elbow. This was partially relieved by salicylates. Four months prior to admission he noticed sensory disturbances in his left arm and in his shoulders, associated with stiffness and pain in his neck. These symptoms were present continuously and were not related to exertion. The past history was noncontributory.

**Physical Examination**—The patient was slightly obese. There was limitation of motion in his neck and in his left shoulder.

**Laboratory Examination**—The red cell count was 5,400,000, with a hemoglobin content of 16.7 Gm per hundred cubic centimeters. The sedimentation rate was 0.2 mm per minute. The total white cell count was 4,700, with a normal differential count. The urine was normal. The Wassermann reaction and the Kahn reaction were negative. The blood level of urea nitrogen was 14 mg per hundred cubic centimeters. Roentgenograms revealed marked tipping of the entire spine, most evident in the cervical portion. The intervertebral spaces were narrowed. The apophyseal joints were normal. There was complete calcification of the anterior ligaments of several vertebral bodies.

**Diagnosis**—The diagnosis was degenerative arthritis of the spine.

**Course of Illness During Hospitalization**—There was no great change in the symptomatology throughout the patient's stay in the hospital. The attacks of pain did become less severe and less frequent. There was no change in the blood picture, and the blood level of urea nitrogen remained the same. No change was noted in the roentgen appearance of the spine.

**CASE 4—History**—A G, a 31 year old white farmer, was admitted to the hospital on Dec 1, 1937. He had been normal up to the age of 18, when for about three months he had suffered with acute pain and swelling in various joints of his body. This condition had then improved, and he had remained symptom free until the age of 23. At that time he had noted sharp, radiating pain in the lower portion of his back and in his hips. Associated with this was a progressive stiffening of the lower portion of his back, which had gradually ascended to involve the entire spine. His back had become fixed in a bent-forward position, and he had become unable to do his farm work because of the pain and deformity. The hip joints were stiff, but the bones did not fuse. The patient stated that he had not had any syphilitic or gonorrheal infection.

**Physical Examination**—The patient was somewhat emaciated and walked with a waddling gait. The thoracic cage was fixed and flattened, and breathing was diaphragmatic. The extremities were normal except for the limitation of motion in both hips, with pain on forced motion. The reflexes were normal. There was marked kyphosis of the entire spine, with the maximum curvature in the dorsal portion. The entire spine appeared to be completely fused.

**Laboratory Examination**—The hemoglobin content was 14.1 Gm per hundred cubic centimeters, with a red cell count of 5,200,000. The sedimentation rate was 0.7 mm per minute. The white cell count was 7,650 with a normal differential count. The blood level of urea nitrogen was 14.0 mg per hundred cubic centimeters. The urine was normal. The Wassermann reaction and the Kahn reaction were negative. Roentgenograms revealed a "bamboo" type of spine, with calcification of the longitudinal ligaments, thinning of the intervertebral spaces and rarefaction of the vertebral bodies. There was complete fusion of the apophyseal and the sacroiliac joints. The articular spaces of the hip joints were narrowed and presented cystic and sclerosing changes in the acetabulum and the head of the femur. There was tipping of the acetabular rim.



*Diagnosis*—The diagnosis was atrophic spondylitis

*Course of Illness During Hospitalization*—During and also following administration of vitamin D there ensued improvement in the patient's appetite. He noted less pain and there was improvement in his gait. On Jan 18, 1938 the sedimentation rate of the blood was 0.9 mm per minute. There was no other change in the blood picture. Roentgenograms revealed no change from those taken on admission.

#### EXPERIMENTAL RESULTS

*Control Period*—Daily samples of food taken from that served to the patients and analyzed at different intervals throughout the entire period of investigation showed the average calcium intake to range from 0.930 to 1.588 Gm per three day period. On this intake the calcium balance remained negative in all 4 patients during the twelve day control period (tables 1 and 2, figs 1 and 2). This negative balance was most evident in M. C., averaging 0.558 Gm on an average three day intake of 0.930 Gm. The lowest average negative balance occurred in A. G., 0.178 Gm on an intake of 1.4 Gm of calcium per three day period. This increased total excretion over the intake of calcium is normal for patients maintained on a low calcium intake.

The phosphorus intake in the food was fairly constant in all 4 patients. The lowest three day intake was that of M. C., 1.924 Gm. The highest intake was that of E. M., 2.235 Gm per three day period. The negative balance shown (tables 1 and 2) in these patients is normal. The highest negative phosphorus balance occurred in E. M., 0.339 Gm (table 2). J. C.'s (fig 1) intake and output were approximately equal.

The urinary excretion of calcium during the control period was within normal limits in all 4 patients. There was considerable individual variation which was not directly related to the amount of calcium ingested in the food. The highest excretion per period, 0.502 Gm, was that of A. G. (fig 2). The excretion by E. M., on a higher calcium intake, was 0.075 Gm (table 2). The fecal excretion of calcium was higher than the intake for 3 patients. A. G.'s fecal excretion was low, 1.076 Gm, while the high urinary excretion compensated and was mainly responsible for the negative balance.

The excretion of phosphorus in the urine was normal in all 4 patients. The lower values were obtained on the older patients. It varied from 1.221 to 1.640 Gm per three day period. The fecal excretion of phosphorus was much lower than the urinary loss. It was related to the phosphorus intake in the food.

The serum calcium was slightly higher in the patients with atrophic spondylitis. In the same patients there was a fluctuation of about 5 per cent in the different determinations made during the control period.

TABLE 1—*Metabolic Data on a Patient with Degenerative Arthritis of the Spine*\*

Period	Date Started	Vitamin D, No of U S P Units per Day	Calcium, Gm				Phosphorus, Gm				Blood			
			Output		Intake in		Output		Intake in		Serum Calcium, Mg / 100 Cc	Serum Phos phorus, Mg / 100 Cc	Serum Phos phatase, King Units/ 100 Cc	Basal Rate, Percent age
			Urine	Feces	Total	Food	Balance	Urine	Feces	Total	Food	Balance		
1	1/8/38		0 124	1 435	1 559	0 930	-0 629	1 235	0 865	2 100	1 924	-0 176	9 5	5 9
2	1/11/38		0 184	1 349	1 533	0 930	-0 603	1 121	0 815	1 936	1 924	-0 012	9 7	9 0
3	1/14/38		0 182	1 320	1 502	0 930	-0 572	1 180	0 742	1 922	1 924	0 002	9 8	10 5
4	1/17/38		0 157	1 199	1 356	0 930	-0 426	1 350	0 623	1 973	1 924	-0 049	9 7	11 0
Average for entire period			0 162	1 326	1 488	0 930	-0 538	1 221	0 761	1 982	1 924	-0 058	9 7	9 1
5	1/20/38	200,000	0 187	1 419	1 606	0 949	-0 637	1 323	0 842	2 165	1 939	-0 226	10 5	11 0
6	1/27/38	100,000	0 206	0 787	1 033	0 968	-0 085	1 080	0 469	1 549	1 954	0 405	9 3	6 0
7	1/26/38	600,000	0 355	1 169	1 524	0 986	-0 538	1 316	0 679	1 995	1 968	-0 027	9 2	15 5
8	1/29/38	1,000,000	0 693	0 595	1 288	1 024	-0 264	1 408	0 467	1 875	1 998	0 123	10 0	13 5
Average for entire period			0 375	0 992	1 367	0 982	-0 385	1 282	0 614	1 896	1 965	0 069	9 7	12 5
9	2/1/38		0 758	0 755	1 513	0 930	-0 583	1 542	0 442	1 984	1 924	-0 060	9 6	8 5
10	2/4/38		0 795	0 689	1 484	0 930	-0 554	1 074	0 600	1 674	1 924	0 250	9 7	11 2
11	2/7/38		0 700	0 516	1 216	0 930	-0 286	1 545	0 416	1 961	1 924	-0 037	10 1	13 4
12	2/10/38		0 677	0 776	1 453	0 930	-0 523	1 079	0 630	1 709	1 924	0 215	8 3	14 0
Average for entire period			0 732	0 684	1 416	0 930	-0 486	1 310	0 522	1 832	1 924	0 092	9 4	11 7

\* Patient M C, a woman aged 57. The diet supplied 2,103 calories and 14 Gm of protein. A high vitamin D intake was followed by increased urinary excretion, decreased fecal excretion and a diminished negative balance of calcium and of phosphorus. There was a slight rise in the serum inorganic phosphorus, without any appreciable change in the serum calcium.

TABLE 2—*Metabolic Data on a Patient with Atrophic Spondylitis*\*

Period	Date Period Started	Vitamin D, No of U S P Units per Day	Calcium, Gm				Phosphorus, Gm				Blood			
			Output		Intake in		Output		Intake in		Serum Calcium, Mg / 100 Cc	Serum Phos- phorus, Mg / 100 Cc	Serum Phos- phate, King, Units/ 100 Cc	Basal Rate, Percent age
			Urine	Feces	Total	Food	Balance	Urine	Feces	Total	Food	Balance		
1	3/11/38		0.082	1.785	1.867	1.588	-0.279	1.524	0.937	2.461	2.235	-0.226	10.4	5.3
2	3/14/38		0.071	1.752	1.823	1.588	-0.235	1.680	0.966	2.646	2.235	-0.411	9.9	5.2
3	3/17/38		0.067	1.933	2.000	1.588	-0.412	1.669	0.977	2.646	2.235	-0.411	9.9	4.1
4	3/20/38		0.085	1.698	1.783	1.588	-0.195	1.689	0.857	2.546	2.235	-0.311	10.1	1.5
Average for entire period			0.075	1.792	1.867	1.588	-0.279	1.640	0.934	2.574	2.235	-0.339	10.1	4.8
5	3/23/38	200,000	0.093	1.611	1.704	1.607	-0.097	1.253	0.901	2.154	2.250	-0.096	9.8	1.7
6	3/26/38	100,000	0.089	1.604	1.693	1.626	-0.067	1.603	0.875	2.478	2.265	-0.213	9.8	1.7
7	3/29/38	600,000	0.162	1.061	1.223	1.615	0.422	1.315	0.614	1.889	2.280	0.391	9.8	1.6
8	4/1/38	1,000,000	0.336	1.756	2.092	1.683	-0.409	1.760	0.913	2.673	2.310	-0.363	11.0	5.1
Average for entire period			0.170	1.508	1.678	1.610	-0.038	1.490	0.808	2.298	2.276	-0.022	10.1	4.8
9	4/4/38		0.390	1.699	1.489	1.588	-0.099	1.679	0.003	2.282	2.235	-0.047	11.3	5.0
10	4/7/38		0.366	1.185	1.581	1.588	0.007	1.868	0.712	2.580	2.235	-0.345	10.3	1.5
11	4/10/38		0.293	1.296	1.529	1.588	0.069	1.537	0.706	2.243	2.235	-0.008	9.7	1.2
12	4/13/38		0.371	1.272	1.643	1.588	-0.055	2.332	0.720	3.052	2.235	-0.817	10.0	3.7
Average for entire period			0.362	1.198	1.560	1.588	0.028	1.851	0.685	2.539	2.235	-0.304	10.3	4.3

\* Patient E M., a man aged 28. The diet supplied 2,040 calories and 58 Gm of protein. The changes in the calcium and the phosphorus balance following a high vitamin D intake are essentially the same as those reported for patient M O (table 1). There was a slight rise in serum calcium, with a fall in phosphatase activity, following the high intake of vitamin D.

The average for the 4 patients varied from 96 to 101 mg per hundred cubic centimeters, which is normal. The inorganic serum phosphorus showed considerable variation, averaging from 3.5 to 4.8 mg per hundred cubic centimeters. These values are within the limits of normal.

In the 2 patients with atrophic spondylitis the phosphatase activity was rather constant. The average of four determinations was 8.4 King

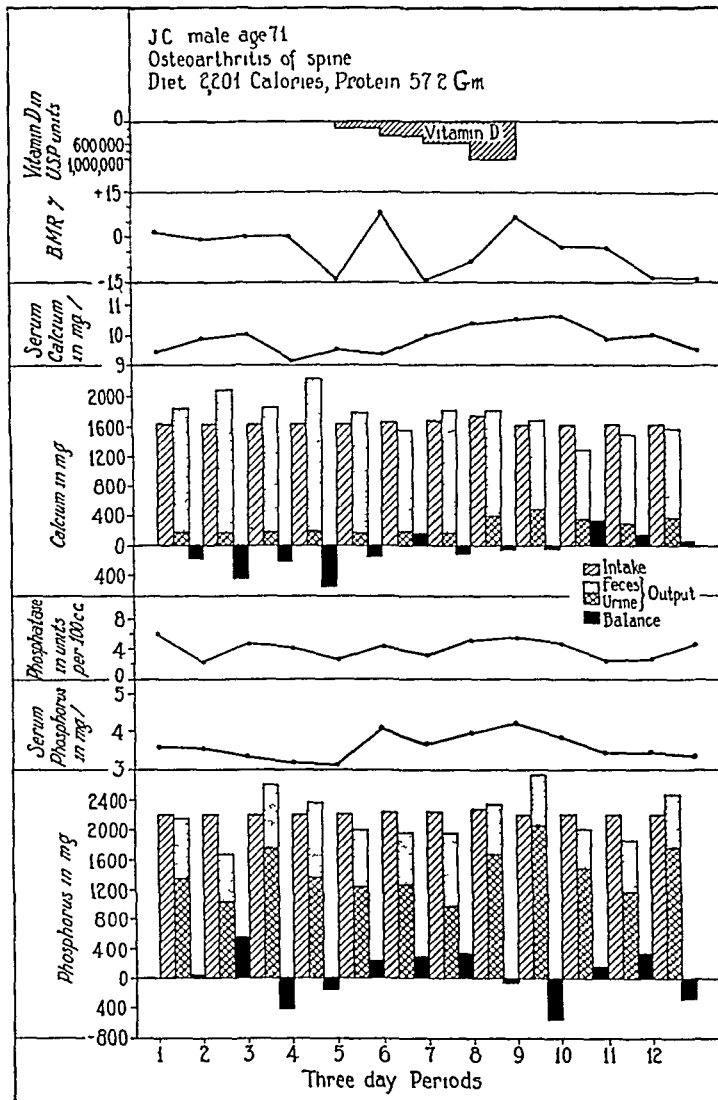


Fig 1 (case 3, J C) —The increased urinary excretion, decreased fecal excretion and diminished negative balance of calcium and phosphorus following the administration of massive doses of vitamin D. There is also a slight increase in serum calcium, serum inorganic phosphorus and phosphatase activity during the period of high vitamin D intake.

units per hundred cubic centimeters of serum in E. M. (table 2) and 8.1 King units per hundred cubic centimeters in A. G. (fig 2). J. C. (fig 1) had the lowest values, with an average of 4.1 King units per hundred cubic centimeters. This is normal for a patient of this age.

group In our laboratory the lowest values have occurred in patients past the age of 60, in whom the phosphatase activity ranges from 20 to 70 King units per hundred cubic centimeters The highest phosphatase activity occurred in M C (table 1), averaging 91 units in four determinations This is above the normal values for patients of this age In our series of over three hundred determinations the average for

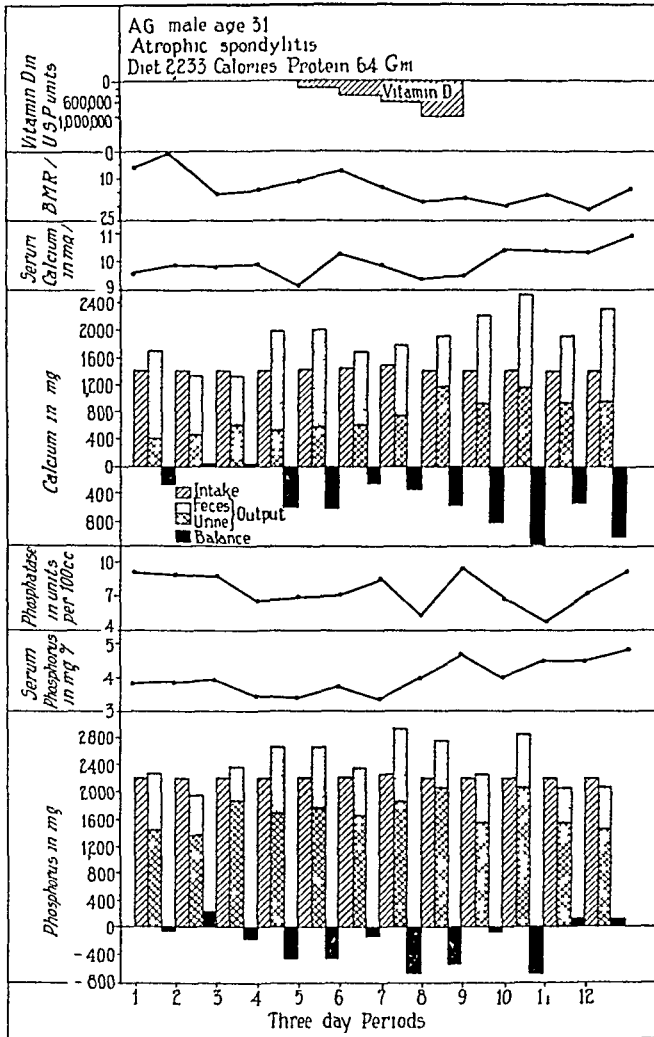


Fig 2 (case 4, A G) —Note how this patient's response to high vitamin D intake differs from that of J C (fig 1) There is a marked increase in the urinary excretion both of calcium and of phosphorus, with a resultant greater negative balance of each The serum calcium and the serum inorganic phosphorus are both increased The basal metabolic rate shows a gradual fall

normal adults is 6.3 units, with a gradual fall in patients past middle life In patients with obstructive jaundice the average phosphatase activity is increased to approximately 20 units and in patients with osteitis deformans the unitage was 50 to 130 per hundred cubic centimeters of

serum depending on the degree of involvement M C had complained of vague pain in the right upper quadrant of the abdomen, a symptom suggestive of disease of the gallbladder. The icteric index was normal. The bromsulphalein test showed normal hepatic function. An intravenous cholecystogram revealed a normal gallbladder. We are otherwise unable to explain the increased phosphatase activity in this patient.

The basal metabolic rates of the 4 patients ranged from  $-15$  to  $+21$  per cent. There was great variation in the individual determinations, and the average for each patient ranged between  $+9$  and  $-9$  per cent during the control period. The third and the fourth determination made during the control period was lower.

*Period of Administration of Vitamin D*—During four three day periods vitamin D was given, beginning with a dose of 200,000 U. S. P. units per day. This was increased by 200,000 units during each of the two succeeding three day periods (figs 1 and 2). During the last period each patient received 1,000,000 units per day. None of the patients showed signs of toxicity, there were no gastrointestinal disturbances. There was no great change in the symptoms during the earlier part of this period. The patients still required analgesics for the relief of pain. During the last three days there ensued an increase in appetite, and the 2 patients with atrophic spondylitis had less discomfort. There was neither loss of weight nor marked change in the clinical picture. The blood pressure remained normal. There was no change in the amount of urine excreted daily.

The changes produced in the metabolism of calcium and phosphorus were striking (tables 1 and 2, figs 1 and 2). Three patients showed a decrease in the negative balance, while A G (fig 2) increased the total excretion both of calcium and of phosphorus in the feces and in the urine, as compared with excretion during the control period.

In all 4 patients there was a marked increase in the urinary excretion of calcium (tables 1 and 2, figs 1 and 2), which reached its highest concentration during the last three days, when the intake of vitamin D was 1,000,000 units per day. The concentration of urinary calcium was increased from 40 to 120 per cent. The urinary excretion of calcium by A G (fig 2) was 1.165 Gm., which approximated the total amount ingested in food. In 3 patients the excretion of calcium in the feces was decreased from 310 to 335 mg. less than during the control period. In A G the fecal excretion of calcium was slightly increased. With the high urinary excretion of calcium there resulted the marked negative calcium balance observed in this patient.

There was a shift in the negative balance of phosphorus toward the positive side in 3 patients, mainly because of a decrease in the fecal excretion of phosphorus. The urinary excretion of phosphorus was diminished in J C and E M, while in M C it showed a small increase.

In A G, however, both the urinary and the fecal excretion of phosphorus was increased, producing a negative balance of 0.446 Gm, as compared with the negative balance of 0.116 Gm during the control period.

There was no appreciable change in the average level of serum calcium during the entire period of administration of vitamin D. In 2 patients it rose slightly during the last three day period, in M C it showed no change, and in A G there was a definite fall in the serum calcium. The serum inorganic phosphorus was increased during the last three day period in all 4 patients.

The serum phosphatase activity showed great variation in all 4 patients. The average activity was decreased in 3 patients and increased in 1, M C (table 1). We are unable to explain this high phosphatase rise. The highest value, 15.5 King units per hundred cubic centimeters, was increased by more than 100 per cent over the normal. The basal metabolic rates were lower than average during this period. The fall, however, was not progressive with the increasing doses of vitamin D.

*Period Following Administration of Vitamin D*—During the last twelve days of investigation the patients did not receive any medication with vitamin D. Slight subjective improvement ensued in the 2 patients with atrophic spondylitis. In J C the attacks of acute pain in the shoulders and arms were less severe and occurred less frequently. There was no change in the condition of M C, and analgesics were continued for the relief of severe pain. There was an increase in the appetites of all 4 patients.

The metabolic effect of vitamin D continued through this period (tables 1 and 2 and figs 1 and 2). In J C the positive calcium balance 0.112 Gm per three day period, continued, while in E M it was 0.028 Gm. M C remained in negative balance, however, this decreased from 0.558 Gm during the control period to 0.486 Gm. In A G there was a further increase in the negative balance, with a loss of 0.833 Gm of calcium per three day period.

The maximum rise in the urinary concentration of calcium occurred during this period, averaging 13.2 mg per hundred cubic centimeters for all 4 patients, as compared with 4.8 mg per hundred cubic centimeters during the control period. The fecal excretion of calcium was low in 3 patients, while in A G it was increased as compared with the control period. The average level of serum calcium was higher in 3 patients during this period. The highest occurred in E M and was 11.3 mg per hundred cubic centimeters. There was no increase in the serum calcium in M C.

The phosphorus balance remained approximately the same as during the control period. There was a slight increase in the urinary excretion of phosphorus but a corresponding decrease in the fecal loss. M C

showed an increase in the retention of phosphorus, with a positive balance of 0.092 Gm per three day period. The other 3 patients remained in negative balance. The average level of serum inorganic phosphorus was increased in 2 patients. In E. M. it was lower, while in J. C. it showed no change.

There was no appreciable change in phosphatase activity, the average values being lower than those observed during the control period, except in the case of M. C., in whom it remained at a high level.

The basal metabolic rates averaged lower in 3 patients and were slightly elevated in J. C. There was no loss of weight or change in pulse rate or blood pressure.

#### COMMENT

Observations made during the control period confirm the assertion of Ropes and associates<sup>9</sup> that there is no primary disturbance of calcium and phosphorus metabolism in patients with degenerative arthritis. We do not know of any metabolic studies on patients with atrophic spondylitis. Golding<sup>18</sup> reported that the serum calcium of patients with this condition was at a high normal level. The 2 patients whose cases we have presented did not show any abnormality in calcium and phosphorus metabolism. The calcium level, the phosphorus level and the phosphatase activity of the serum were essentially normal, as was the urinary excretion of calcium. These circumstances would appear to rule out parathyroid dysfunction both in degenerative arthritis of the spine and in atrophic spondylitis.

Nicolaysen<sup>19</sup> has shown that vitamin D increases the absorption of calcium from the intestinal tract of rats. He reported that the slightly increased absorption of phosphorus is due to this increased absorption of calcium. We conclude that the decreased fecal excretion of calcium in 3 patients during the period of high vitamin D intake and in the subsequent period is due to the increased absorption of calcium from the intestinal tract. This increased absorption was rather constant in 3 patients and averaged 0.284 to 0.335 Gm per period. However, there was an increased loss of calcium in the urine, this factor appearing to be responsible for maintaining the serum calcium at the normal level.

So far as we are aware, there is not as yet any accurate quantitative clinical measurement of the circulating parathyroid hormone. In patients

18 Golding, F. C. Spondylitis Ankylopoietica, *Brit. J. Surg.* **23** 484 (Jan) 1936.

19 Nicolaysen, R. Studies upon the Mode of Action of Vitamin D. II. The Influence of Vitamin D on the Fecal Output of Endogenous Calcium and Phosphorus in the Rat, *Biochem. J.* **31** 107 (Jan) 1937, III. The Influence of Vitamin D on the Absorption of Calcium and Phosphorus in the Rat, *ibid.* **31** 122 (Jan) 1937.



without primary disturbance of the calcium and phosphorus metabolism (and with normally functioning liver and kidneys) an alteration in the activity of the parathyroid glands may be reflected in the phosphatase activity of the serum. With an associate we<sup>20</sup> have observed low phosphatase activity in the serum of a patient with chronic hypoparathyroidism. This was corrected, and the activity remained at higher normal levels after a successful transplanting of parathyroid tissue culture, as shown by subsequent clinical and metabolic studies.<sup>20</sup> Hanson and associates<sup>21</sup> and also Albright and Sulkowitsch<sup>8</sup> observed a decrease in the serum phosphatase after administration of massive doses of vitamin D. In 3 of our patients there was a slight fall in the serum phosphatase activity.

It is difficult to explain the different response of A. G. to large doses of vitamin D. During the control period he had the highest average urinary excretion of calcium. On the administration of vitamin D the percentage increase in the concentration of the urinary calcium was approximately the same as the average of the other 3 patients, however, the total urinary output of calcium rose to a much higher level. It was 1.163 Gm. per three day period at its maximum excretion. This was almost as high as his calcium intake. With the slight increase in fecal excretion of calcium this resulted in a negative balance of — 1.102 Gm. for one period. He also differed from the other 3 patients in that the urinary excretion of phosphorus was greatly increased during the twelve days of high vitamin D intake. Albright has suggested that vitamin D may exert an influence on the excretion of phosphorus similar to that of the parathyroid hormone, causing the skeletal demineralization encountered in certain cases of hypervitaminosis D. Such an effect was undesirable in the case of A. G., who had generalized bone atrophy, as shown by roentgen examination.

Vitamin D as administered in this investigation did not produce any demonstrable changes in the activity of the thyroid. The basal metabolic rate dropped slightly. However, this drop was similar to that observed in normal persons subjected to repeated determinations of the basal metabolic rate. It was apparently due to training and the better cooperation of the patients during the latter part of the investigation.

There was an increase in the appetite of all 4 patients during and also after the administration of high vitamin D. This suggests an increased activity of the thyroid. However, there was no change in

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20 Houghton, B. C., Klassen, K. P., and Curtis, G. M. Studies in Human Parathyroid Transplantation, *Ohio State M. J.* **35** 505 (May) 1939.

21 Hanson, A. E., McQuarrie, I., and Ziegler, M. R. Effects of Parathyroid and of Vitamin D on Blood Phosphatase, Calcium and Phosphorus in Osteogenesis Imperfecta, *Endocrinology* **22** 1 (Jan) 1938.

body weight, pulse rate or blood pressure. The excretion of iodine in the urine, as revealed by urinalyses for iodine, was not increased in these patients. Curtis and Puppel<sup>22</sup> have demonstrated an increased loss of iodine in the urine in the majority of patients with untreated hyperthyroidism. Our patients were all maintained on a constant, controlled, low iodine diet. It would appear that increased function of the thyroid would have been reflected in an increased excretion of iodine in the urine.

Reed and his associates<sup>23</sup> observed an increase in the metabolic rate of dogs and of rats after the administration of subtoxic doses of vitamin D. Since no such results were obtained in thyroparathyroidectomized dogs,<sup>24</sup> these investigators concluded that vitamin D produced its calorigenic effect through the thyroid. We did not obtain any evidence in this investigation to support their conclusions.

Certain data suggest that the beneficial results of the administration of large doses of vitamin D are due to the resultant increased concentration of the serum calcium. Thus, Brunschwig<sup>25</sup> has shown that the injection of calcium gluconate intravenously diminishes the pain in patients with metastatic carcinoma of the skeleton.

We observed that the subjective improvement of 3 patients coincided with the rise in the serum calcium, while the fourth, M. C. (table 1), who had no such rise, did not notice any change in her symptoms. The slight increase in motion of the hips in 2 patients might be explained on the basis of decreased pain. Roentgenograms did not reveal corresponding changes in the appearance of the articular surfaces or spaces.

Hubbart<sup>26</sup> in reviewing the literature on hypervitaminosis D warned against the indiscriminate use of vitamin D in the treatment of patients. Vitamin D given in toxic doses is said to produce cell degeneration and calcification. Determining factors are the possible sensitivity of certain patients to this vitamin, the dose administered, the duration of treatment and the calcium, possibly also the phosphorus, intake. The elevation of the serum calcium was but small in our patients, yet the urinary excretion of calcium was increased far above the normal physiologic level. In the presence of renal damage, infection or alkaline reaction of the urine

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22 Curtis, G. M., and Puppel, I. D. Increased Urinary Iodine of Hyperthyroidism, *Arch. Int. Med.* **60**: 498 (Sept.) 1937.

23 Reed, C. I., Thacker, E. A., Dillman, L. M., and Welch, J. W. The Effect of Irradiated Ergosterol on the Metabolism of Normal Dogs, *J. Nutrition* **6**: 355 (July) 1933. Reed, C. I. Effect of Heavy Administration of Viosterol on Metabolism of Rat, *Proc. Soc. Exper. Biol. & Med.* **32**: 274 (Nov.) 1934.

24 Deutsch, H., Reed, C. I., and Struck, H. C. The Role of Thyroid in the Calorigenic Action of Vitamin D, *Am. J. Physiol.* **117**: 1 (Sept.) 1936.

25 Brunschwig, A. Observations on the Administration of Large Doses of Calcium in Metastatic Carcinoma in Bone, *Am. J. Cancer* **25**: 721 (Dec.) 1935.

26 Hubbard, A. W. Hypervitaminosis D, *Illinois M. J.* **72**: 253 (Sept.) 1937.

deposition of calcium in tubules or calices certainly might occur. The concentration of the urinary calcium in 1 of our patients was as high as is encountered in patients with hyperparathyroidism.

The number of patients is too small to draw any conclusions as to the efficacy of vitamin D in the treatment of chronic arthritis. There are in the literature, however, reports covering large series of cases.<sup>27</sup> We agree with Irons<sup>1</sup> and Hubbard<sup>26</sup> that vitamin D in massive doses should be used with caution and only in patients who are under close observation and are followed by frequent laboratory examination not only of the serum calcium but of the concentration of calcium element in the urine.

#### SUMMARY

Complete studies of calcium and phosphorus metabolism were made on 2 patients with atrophic spondylitis and 2 patients with degenerative arthritis of the spine before, during and subsequent to the administration of massive doses of vitamin D.<sup>15</sup>

There was no primary disturbance in the calcium and phosphorus metabolism in the patients with atrophic spondylitis or with degenerative arthritis of the spine.

The administration of massive doses of vitamin D resulted in an increased retention of calcium in 3 patients, while the negative calcium balance of 1 was increased. The urinary excretion of calcium was increased for all 4 patients. The fecal loss of calcium of 3 patients was decreased, and that of 1 was increased. Three patients had a slight rise in the concentration of serum calcium.

Subsequent to the administration of vitamin D a slight increase in phosphorus retention ensued in 3 patients, while 1 showed an increase in the loss of phosphorus. The urinary excretion of phosphorus was increased for all 4 patients, while the fecal excretion of 3 was diminished and that of 1 was slightly increased. The serum inorganic phosphorus was elevated in 3 patients. The phosphate activity of the serum was slightly decreased in 3 patients.

Vitamin D in massive doses as administered in this investigation did not produce demonstrable changes in the activity of the parathyroids or the thyroid.

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27 Hench, P. S., Bauer, W., Fletcher, A. A., Christ, D., Hall, F., and White, T. P. The Problem of Rheumatism and Arthritis. Review of American and English Literature for 1935 (Third Rheumatism Review), *Ann Int Med* **10** 754 (Dec) 1936. Hench, P. S., Bauer, W., Christ, D., Hall, F., Holbrook, W. P., Key, J. A., and Slocumb, C. H. The Present Status of Rheumatism and Arthritis. Review of American and English Literature for 1936 (Fourth Rheumatism Review), *ibid* **11** 1089 (Jan) 1938.

another died two days after feeding. Of 2 animals receiving 1,320 mg per kilogram, 1 was unable to walk for an hour and the other remained sick and weak for twenty-four hours. One animal after a feeding of 1,760 mg per kilogram sprawled out immobile for a long time.

Feedings continued for five to seven days failed to produce any effect in 4 animals receiving 44 mg per kilogram per day. Of 4 receiving 165 mg per kilogram per day, 1 died on the sixth day, and of 14 receiving 220 mg per kilogram per day, 1 died, probably because of being tube fed while the stomach was distended with food.

The immediate effects of inhalation of pyridine noted in man have included flushing of the face, quickening of the pulse and respiration, temporal headache, a full sensation of the head approaching giddiness and a desire to sleep.<sup>8</sup> After eight days' treatment 1 asthmatic patient experienced nausea and vertigo.<sup>9</sup> Lublinski<sup>10</sup> reported a case in which there was marked tremor of the limbs with nausea and another in which there were vomiting, dizziness and severe headache. In all cases the effects followed inhalations lasting one to one and a half hours. More serious effects were noted by Ludwig<sup>11</sup> when crude pyridine containing impurities of picoline, lutidine and collidine was inhaled over a considerable period by employees in two chemical works. Among the lesser symptoms observed were headache, vertigo, abdominal pain, heart burn, vomiting, disturbed sleep, weakness, giddiness, anorexia and nervousness.

There were 2 instances of serious effects. In 1 case transient paralysis of the facial nerve, periods of unconsciousness, ataxia and unequal pupils developed. Urobilinogen was excreted in the urine, and bilirubin was found in the serum in an amount of 2.15 mg per hundred cubic centimeters.

In the second case of serious complication a 37 year old man had worked with crude pyridine off and on for two years, when headache, vertigo, nausea, anorexia and insomnia developed. Then suddenly paralysis of the right facial nerve ensued, and two days later there developed partial paralysis of the left oculomotor nerve, paralysis of the abducens nerves, partial paralysis of the palate, absence of the gag reflex and paralysis of the recurrent laryngeal nerves. There were cerebellar ataxia on the right side, thermanesthesia and slight hemiparesis of the right side. The level of urobilin was increased in the urine but was normal in the blood.

The patient's condition was interpreted by Ludwig to be the result of pseudoencephalitis of Wernicke. After three months the symptoms and signs largely disappeared.

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8 Neff, J. S. *New York M. J.* **43** 299, 1886.

9 See, G. *Bull. gen. de therap.* **108** 529, 1885.

10 Lublinski, W. *Deutsche med. Ztg.* **2** 985, 1885.

11 Ludwig, H. *Arch. f. Gewerbepath. u. Gewerbehyg.* **5** 654, 1934.

characteristic odor, it is miscible with water and with alcohol and boils at 115 C

The fate of pyridine in organisms was first studied by His<sup>3</sup> (1887), who found that in dogs it is excreted as methylpyridyl ammonium hydroxide

For the most part the studies on its effects on living organisms have been conducted on frogs Brunton and Tunnichiffe<sup>4</sup> claim that the depressant effect on the nervous system of frogs is mainly confined to the sensory system, mostly in the spinal cord and that large doses depress the respiratory center In frogs large doses produce convulsions Although large doses paralyze cardiac muscle, ordinary ones do not depress the heart, and with systemic administration Brunton and Tunnichiffe said, "The heart was the last organ to die" In man pyridine is said to increase the power of the cardiac contraction and raise the tension<sup>5</sup>

As to its toxicity, von Oettingen<sup>6</sup> stated that it is not marked Distler<sup>7</sup> reported that in rabbits orally administered doses of 2 Gm per 1.5 Kg caused only slight depression and twice this dose caused marked depression and killed the animals by paralysis of the respiratory center The minimal fetal dose for guinea pigs was reported by Brunton and Tunnichiffe as 87 mg per hundred grams with intraperitoneal injection and as 400 mg per hundred grams with oral administration His<sup>3</sup> administered 0.1 Gm daily in the form of a 5 per cent solution to dogs for thirty-five days without observing any toxic symptoms aside from occasional vomiting and diarrhea

Pyridine in the doses administered to rabbits during our study of its anticonvulsant property caused only evanescent immediate effects and these in only a few animals Of 39 animals receiving an intravenous injection of 110 mg of pyridine per kilogram of body weight, 3 immediately sprawled out and remained in a hypotonic, ataxic parietic state for no longer than three minutes, then entirely recovered Sialorrhea was observed occasionally Of 7 receiving 220 mg per kilogram, 4 sprawled out for less than three minutes

Single feedings of 220 to 660 mg per kilogram, inclusive, failed to produce any effect with one exception of sprawling shortly after 220 mg was administered Of 12 animals receiving 880 mg per kilogram, 1 was immobile for a time, another startled easily, 1 died four days later and

3 His, W Arch f exper Path u Pharmacol **22** 253, 1887

4 Brunton, T S, and Tunnichiffe, F W J Physiol **17** 272, 1894

5 De Renzi, E Riv clin e terap **8** 169, 1886

6 von Oettingen, W F The Therapeutic Agents of the Pyrrole and Pyridine Group, Ann Arbor, Mich, Edwards Brothers, Inc, 1936

7 Distler, H Ueber einige Wirkungen des Pyridin, Inaug Dissert, Erlangen, Junge & Sohn, 1887

occasional headache, faintness, fatigue, weakness, mental depression and often restless sleep

The blood picture as reflected by numerous examinations showed a tendency to a decrease in the number of leukocytes in the 5 patients from 9,000 to 6,000, from 9,500 to 6,000, from 9,500 to 5,000, from 6,000 to 5,000 and from 10,000 to 8,200, respectively. There was a tendency for an increase in the percentage of eosinophils in 3 patients, from 1 to 9, from 0 to 6 and from 8 to 12, respectively. In 1 patient there was no change and in another a decrease from 5 to 2 per cent. Occasionally, an increase of basophils was encountered. Vacuolation ordinarily reported as being seen in the red cells of experimental animals, was noted in eosinophilic leukocytes in 2 patients, in 2 patients there was a slight increase in the number of lymphocytes. Otherwise, there was no change in the number of red cells, the concentration of hemoglobin, the coagulation time, the bleeding time or the sedimentation rate.

Little or no free hydrochloric acid was found in the stomach before treatment was begun, and no change was observed after treatment.

The feces did not show any change, and bowel movements were not increased. The urine of 1 patient, who later became violently ill and died, was normal throughout the medication with pyridine. In the urine of 3 patients erythrocytes were encountered in small numbers, in that of 2 a trace of albumin was present before treatment and did not increase, and in that of 1 for whom treatment was discontinued a few hyaline casts were found before treatment and at the end of ten days when treatment was discontinued. The results of phenolsulfonphthalein excretion tests did not show any change from normal. The amounts of calcium, sodium, potassium, chlorides, nonprotein nitrogen and urea nitrogen in the blood remained constant and within normal limits, as was the case with the carbon dioxide capacity, the result of the van den Bergh test, the icterus index and the result of the hippuric acid test of hepatic function. Results of repeated galactose tolerance tests on 4 patients showed that in 1 the total amount excreted was 6.5 Gm before treatment was instituted and 1.8 Gm after twenty-eight days' treatment; in the other 3 patients the amount excreted was quite below normal limits before treatment and fell from 2.8 to 1.8 Gm, from 2.38 to 1.4 Gm and from 2.6 to 1.56 Gm, respectively.

In all of the patients before treatment the phosphatase value was at a high normal level and fell after treatment from 5.5 to 1.7 King units per hundred cubic centimeters, from 4.9 to 2.36 units, from 5.57 to 2.84 units and from 4.9 to 3.9 units, respectively, in the adults and from 8.8 to 5.1 units in a boy 16 years old.

The blood level of inorganic phosphorus was within normal limits in all 5 patients before treatment and was increased in the 4 adults from 2.76

We did not find any reports of toxic effects other than heart burn and occasional nausea following the use of pyridine in the doses ordinarily prescribed by mouth, 6 to 25 minims

However, Helme<sup>12</sup> reported a case in which accidental swallowing of half a cupful of commercial pyridine resulted in death in forty-three hours. After the ingestion the patient vomited five times in seven hours, when admitted to the hospital he was pale and slightly cyanosed, with a temperature of 103.4 F, a pulse rate of 128 per minute and a respiratory rate of 40 per minute. He complained of a choking sensation, precordial pain, abdominal pain and inability to swallow. Acute congestion of the lungs, bronchitis and purulent expectoration developed, and the patient became wildly delirious and died. Examination of the urine failed to reveal any abnormality, and at autopsy no changes in the heart, kidney or spleen were encountered. The liver had a few fatty patches. The chief lesions were those of the epiglottis, trachea, bronchi, lungs, esophagus and stomach.

#### EFFECT OF ADMINISTRATION OF PYRIDINE TO FIVE PATIENTS SUFFERING FROM EPILEPSY

Five patients suffering from epilepsy were admitted to Passavant Memorial Hospital and placed in a special ward during the period of study. Prior to the administration of pyridine the first few days to a week of hospitalization were occupied by a battery of tests devised to reflect any visceral, chemical or blood changes, and after medication with pyridine was begun, these were repeated at weekly intervals. During most of the period the patients were allowed to take their previous medication of sodium bromide, phenobarbital or dilantin sodium alone or in combination. To 2 patients pyridine was administered for ten days, to 2 others for twenty-eight days and to another for thirty days. After discharge from the hospital the fifth patient continued to take pyridine for seven days, he took none for forty days and then took it again for twenty-five days, when he became seriously ill. One who had taken it for twenty-eight days in the hospital continued for fifty additional days, without noticeable toxic effect. Administration of pyridine to the other patients was discontinued.

We did not observe any change in temperature, pulse, respiration or blood pressure during the administration of pyridine in doses of 10 minims (0.6 cc) occasionally three times but usually four times a day. There was an increase of body weight of 1 to 6 pounds (0.5 to 3 Kg). At one or another time there were complaints of a minor nature of anorexia, eructations, nausea, occasional vomiting, gastric distress, fullness, occasional pain or pressure in the abdomen, abdominal distention

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<sup>12</sup> Helme, G. E. Brit. M. J. 2: 844, 1893

TABLE 1—Chemical Changes in the Blood of Five Patients with Epilepsy Taking Pyridine During a Month's Experiment to Determine the Anticonvulsant Effect of This Compound

Patient	Date	Non protein Nitro gen, Mg./ 100 Cc	Icterus Index, Units	Choles terol, Mg./ 100 Cc	Choles terol Esters, Mg./ 100 Cc	Total Pro tein, Gm./ 100 Cc	Albu min, Gm./ 100 Cc	Glob ulin, Gm./ 100 Cc	Phos phorus, Mg./ 100 Cc	Calcium, Mg./ 100 Cc	Chlo rides, Mg./ 100 Cc	Phos phorus, King Units/ 100 Cc	Sodium, Mg./ 100 Cc	Potas sium, Mg./ 100 Cc	Urea Nitro gen, Mg. of 100 Cc	Hip puric Acid, % of Normal	Carbon Reaction, Dioxide Capac ity, %	Reaction, Mg. of Bilirubin /100 Cc
Patient 1 (case 1)	1/29	30.8	5	214	141	5.66	4.6	1.06	2.76	10.41	168	5.59	341	19.6	12.5	141.5	47.5	0.5
	5/14	32.2	6	192	133	6.6	5.28	1.32	2.94	9.62	470	3.12	336	21	12.5	130.5	60	0.5
	5/21	22.6	7	179	119	7	5.33	1.67	3.12	10.05	472	2.99	348	21	12.2	126	51.7	1.56
	5/27	31.2	7	170	121	6.25	4.8	1.45	3.2	9.7	460	1.7	345	24.4	11.3	133	54.2	0.85
Patient 2	5/1	37	7	100	289	6.14	4.84	1.6	2.86	10.48	464	1.9	342	29.6	11.7	109	48	0.5
	5/14	35	7	295	206	6.93	5.25	1.68	4	10.05	454	3.74	342	21.3	13.2	129	47.3	0.5
	5/21	25.4	7	277	177	7.04	5.39	1.65	3.8	10.28	470	2.4	347	21	10.9	133	50.5	0.5
	5/27	28.9	6	205	128	7.13	5.02	2.11	3.04	10.2	455	2.36	347	23.2	8.7	132	53.1	0.5
Patient 3	1/29	31.1	7	197	127	6.25	5.15	1.1	2.86	10.82	424	5.57	334	22.1	15.4	125	51.8	0.85
	5/14	27.8	7	232	142	7.2	5.44	1.76	3.41	10.7	470	3.34	335	20.8	9.15	136	54.6	0.5
	5/21	24.2	6	200	123	7.5	5.26	2.25	3.62	10.8	470	2.74	347	22.3	10.9	111	51.5	0.5
	5/27	30.6	6	186	125	6.87	5.44	1.43	3.16	9.75	475	2.84	338	20.8	9.8	136	54	0.5
Patient 4	5/20	31.6	5	196	134	7.02	4.8	2.22	5.66	10.62	450	8.84	342	23.2	11.1	104	56.8	0.5
	5/27	30.1	5	192	117.8	6.91	5.23	1.68	3.8	10.2	475	5.1	337	19.8	9.6	126	53.1	0.5
Patient 5	1/29	38.8	7	318	239	5.57	4.45	1.12	2.88	10.82	432	4.92	336	21.9	17.8	125	56.8	0.5
	5/14	29.2	7	285	203	7.2	4.9	2.3	3.49	10	450	3.9	348	21.9	11.7	110	51.9	0.85



to 32 mg per hundred cubic centimeters, from 286 to 304 mg, from 286 to 316 mg and from 288 to 349 mg, respectively, all increases being within normal limits. In the case of the boy it fell from 566 to 38 mg per hundred cubic centimeters.

In 4 patients the blood level of cholesterol in milligrams per hundred cubic centimeters fell from 214 to 170, from 400 to 205, from 197 to 186 and from 318 to 285, respectively. In 1 patient it remained about the same, decreasing from 196 to 192 mg per hundred cubic centimeters. The cholesterol esters in milligrams per hundred cubic centimeters were diminished in the same sequence from 141 to 121, from 298 to 128, from 127 to 125, from 239 to 203 and from 134 to 117, respectively.

There was a slight increase of serum total protein within normal limits in 4 patients from 5.6 to 6.2 Gm per hundred cubic centimeters from 6.4 to 7.13 Gm, from 6.2 to 6.8 Gm and from 5.57 to 7.2 Gm, respectively, and a decrease in 1 from 7.02 to 6.9 Gm. At the same time the globulin fraction was somewhat increased in the first 4 patients in the same order from 1.06 to 1.45 Gm per hundred cubic centimeters, from 1.6 to 2.11 Gm, from 1.1 to 1.43 Gm and from 1.12 to 2.3 Gm, respectively, and decreased in the fifth patient from 2.22 to 1.68 Gm, all changes being within normal limits.

From this study it was concluded that there was no evidence of damage to any organ and that with the exception of some minor subjective complaints and gastrointestinal disturbances the administration of 10 minims of pyridine four times a day did not produce any toxic effect. Therefore, treatment of 2 patients was continued, and medication was started for another patient, who had not been studied in the hospital. In 2 of them conditions developed which we feel were the result of damage produced by pyridine.

#### REPORT OF TWO CASES

**CASE 1—Summary**—During medication with pyridine in doses of first 30 minims (1.85 cc), then 40 minims (2.46 cc), a day abdominal pain, nausea, vomiting, headache and anorexia suddenly developed in a young man suffering from a convulsive disorder. Jaundice and edema of dependent parts followed. Hiccups accompanied the symptoms just mentioned. There was a mild fever. Azotemia and albuminuria progressed. Death ensued eight days after the onset of the acute symptoms. The condition appeared to be of hepatic and renal origin.

**Detailed Report**—O. G., a white man aged 32, was first admitted to the Montgomery Ward Medical Clinics of Northwestern University Medical School on May 9, 1938. Nothing in his familial or personal history was pertinent to his illness. The first attack of a convulsive seizure occurred at the age of 15, while he was on a "high ride" in an amusement park. Attacks then were repeated with increasing frequency, so that in 1933 he was having one or more attacks daily. In addition, attacks of petit mal occurred one to three times a week. The attacks were not preceded by an aura, nor did they begin with any motor disturbance indicating a focal lesion. Neurologic examination, as well as all other examina-

discoloration of the feet appeared. Respiration was difficult, and moist rales were heard over the bases of the lungs. On August 26, the blood contained 116 mg of non-protein nitrogen per hundred cubic centimeters and the icterus index was 50, the urine continued to contain large quantities of albumin. On August 27 as the jaundice increased the patient became more drowsy and vomited more frequently, the vomitus contained blood (4 plus) as indicated by the result of the benzidine test. Edema of the face increased, the patient became irrational at times, the abdomen was tympanitic, and respirations increased to 38 per minute. Diuresis was not brought about by administration of theophylline with ethylenediamine. On August 28 the patient was in a deep stupor. The subconjunctival hemorrhages were increased, and generalized edema was present. On chemical examination the blood per hundred cubic centimeters contained 175 mg of nonprotein nitrogen, 125 mg of cholesterol, 20 mg of cholesterol esters, 4.77 Gm of albumin, 1.94 Gm of globulin, 106 mg of urea, 6.57 mg of phosphorus and 6.33 King units of phosphatase. The icterus index was 28. The urine per hundred cubic centimeters contained 164 mg of urea and 21 mg of ammonia nitrogen. It contained albumin (4 plus) but no casts. The nitrogen urea clearance was 13 cc in one hundred and twenty-three minutes.

On August 28, in spite of intravenous injection of fluid and administration of theophylline with ethylene diamine, prostigmine methylsulfate, oxygen and stimulants, the patient died. Permission for autopsy was refused.

**CASE 2—Summary**—After eleven days of administration of pyridine in doses of 30 minims per day stupor developed in a young man aged 35 suffering from a convulsive disorder due to an astrocytoma successfully treated by removal and roentgen therapy. Evidence of hepatic involvement and renal insufficiency was discovered, and during the period of illness residual focal signs of brain disease increased and aphasia and agnosia developed. After a month of severe illness the patient began to improve, and he recovered completely from the hepatic involvement and renal insufficiency and the temporary increase of cerebral disability.

**Detailed Report**—W. K., a white man aged 35, was admitted to the Montgomery Ward Medical Clinics of the Northwestern University Medical School in November 1936. He had had his first convulsive seizure at the age of 31. Seizures had continued in the form of four to five attacks of petit mal daily and one to three attacks of grand mal monthly. An aura of premonition preceded these attacks. Four years later right hemiparesis and right homonymous hemianopia had developed, and the patient was operated on by Dr. Howard Naffziger. An astrocytoma of the left parieto-occipital lobe was removed, and removal was followed by roentgen therapy. The patient had continued to have convulsive seizures, but few residual signs of an organic lesion remained, namely, slight right hemiparesis with incomplete right homonymous hemianopia. Despite therapy with bromides, phenobarbital and dilantin sodium, the attacks had continued, although they were markedly diminished.

On Aug. 2, 1940 the patient was placed on a treatment schedule of 10 minims of pyridine three times a day with  $1\frac{1}{2}$  grains of phenobarbital four times a day. On August 12 he reported a little nausea after taking the pyridine. On August 16 his aunt reported that he had become increasingly stuporous during the preceding three days. He was sent to the Cook County Hospital that day.

On examination the patient was somewhat stuporous and appeared rather indifferent but cooperative and oriented. The temperature was 98 F, the respiratory rate 20 per minute and the blood pressure 110 systolic and 70 diastolic. The pupils were unequal, the right one being smaller than the left one, but both reacted well to light directly and consensually and in accommodation. There was a fine

tions, failed to reveal any abnormality. Although during administration of sodium bromide attacks of grand mal had been stopped for six months at one time, they recurred and were then, as were the attacks of petit mal, recalcitrant to treatment by bromides, phenobarbital and dilantin sodium.

On April 29, 1940, the patient was admitted to the Passavant Memorial Hospital. For twelve days he was given 30 minims (1.85 cc) of pyridine a day and for an additional eighteen days 40 minims (2.46 cc) a day. No significant changes in bodily function indicative of any toxic effect were noted.

After his discharge from the hospital on June 14 he was again placed on a treatment schedule of 10 minims of pyridine three times a day and  $1\frac{1}{2}$  grains (0.09 Gm) of phenobarbital four times a day. On June 21 his supply of pyridine was exhausted, and since he had suffered from acute pharyngitis, no more pyridine was prescribed. Three days later, after taking magnesium sulfate, the patient experienced a pain in the lower part of the abdomen. He was admitted to the Cook County Hospital on June 25. His condition was given the diagnosis of diverticulitis, within a few days the symptoms subsided, and he was discharged on June 29.

On July 29 he was again placed on a treatment schedule of 10 minims of pyridine three times a day and  $1\frac{1}{2}$  grains of phenobarbital four times a day. On August 20 he was awakened from sleep by a sharp pain in the right side of the abdomen. He vomited soon after, then felt chilly and feverish. A headache of a dull nature was noted. The next day the abdominal pain, headache and vomiting continued. Diminished urinary output was noted, only a small amount of dark urine having been passed on the second day of illness. On the third day, the symptoms continued and hiccuping developed. During these three days he had had only one bowel movement, with a watery stool. On the third day he was admitted to the Cook County Hospital. The temperature was 101 F, the pulse rate 120 per minute, the respiratory rate 24 per minute and the blood pressure 110 systolic and 60 diastolic. The patient's tongue was coated and his breath foul, he hiccuped frequently and occasionally vomited. There was dullness in the middle lobe of the right lung, and rales were heard over this area. Roentgenograms of the chest showed the diaphragm was elevated on the right side. A specimen of urine obtained by catheterization contained albumin (4 plus) but neither blood nor bile. On August 23 examination of the blood showed that per hundred cubic centimeters it contained 89 mg of nonprotein nitrogen, 13 mg of uric acid, 104.6 mg of urea, 7.5 mg of creatinine, 3.37 Gm of albumin, 1.58 Gm of globulin, 131 mg of cholesterol, a trace of cholesterol esters, 5.15 mg of phosphorus, 6.55 King units of phosphatase and 400 mg of chlorides. Slight secondary anemia and leukocytosis (17,100 cells) were present. Per hundred cubic centimeters the urine contained 100 mg of urea, 13.7 mg of ammonia nitrogen and 24 units of diastase.<sup>12a</sup> Albumin (4 plus) was present in the urine, and urea clearance was 9 cc in one hundred and sixty-one minutes.

On August 24 the patient appeared worse. His scleras and skin were icteric. There was marked tenderness in the abdomen, and hepatic dullness seemed increased. A Levine tube was introduced, and solutions of dextrose and sodium chloride were given intravenously. On August 25 his temperature was 99.6 F and his blood pressure was 108 systolic and 60 diastolic. He appeared acutely ill. Subconjunctival hemorrhages appeared in the left eye. Edema of the eyelids and the

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<sup>12a</sup> The unit of diastase used is the one commonly employed in the United States. One unit represents the quantity of urine in cubic centimeters that will convert a 0.1 per cent starch solution to sugar in half an hour at 37 C. Normal is 8 to 32.

horizontal nystagmus. The patient's speech was slow and slurred, and his responses were slow. All deep reflexes were brisk bilaterally, and superficial abdominal and cremasteric reflexes were normal. No pathologic reflexes were elicited. Examination of the fundi revealed a questionable blurring of both optic disks. Gross tests of the visual fields revealed right homonymous hemianopia. Examination of the spinal fluid revealed a clear but xanthochromic fluid under normal pressure, containing 4 cells per cubic millimeter, per hundred cubic centimeters it contained 57 mg of total protein, 75 mg of sugar and 680 mg of chlorides. The urine showed albumin (4 plus) and 10 to 20 white blood cells per low power field, no casts were observed. The blood per hundred cubic centimeters contained 8.5 mg of uric acid and 139 mg of nonprotein nitrogen. On August 20 there was a weakness in the right lower extremity, the deep reflexes of this extremity were greater than those of the left one. The right side of the face moved with less facility than the left side. Movements of the right upper extremity were clumsy. There was considerable stupor. On August 22 the blood level of nonprotein nitrogen was 137 mg per hundred cubic centimeters, and there was marked albuminuria. On August 23, the icterus index was 11 and the blood per hundred cubic centimeters contained 9.7 mg of uric acid, 13 mg of creatinine, 5.85 Gm of total protein, 4.3 Gm of albumin, 1.55 Gm of globulin, 165 mg of cholesterol and 170 mg of nonprotein nitrogen. On August 27 there were present anomia, ataxia, acalculia, defect in body scheme, confusion and disorientation. The patient's tongue was heavily coated and his breath urinous. It became necessary to restrain him in bed. On August 30 he had epileptiform seizures, occasionally right sided, at other times generalized. From day to day he seemed to become worse, the confusion increased, and he refused to eat or to talk with visitors and became belligerent and excited. On September 7 the blood per hundred cubic centimeters contained 155 mg of nonprotein nitrogen, 4.7 mg of uric acid, 5.4 mg of creatinine, 166 mg of cholesterol and 46 mg of cholesterol esters. A blood transfusion was performed on September 10. Two days later the patient began to show signs of recovery, and a week later he was able to converse intelligently. On September 18, the icterus index was 15 and the blood per hundred cubic centimeters contained 41 mg of nonprotein nitrogen, 5.98 Gm of total protein, 333 mg of phosphorus, 9.6 mg of calcium, 178 mg of cholesterol and 120 mg of cholesterol esters. On September 22 these blood levels had further decreased per hundred cubic centimeters to 32 mg of nonprotein nitrogen, 2.3 mg of uric acid and 2 mg of creatinine, and the blood contained 1.1 mg of phenol per hundred cubic centimeters (table 2). On October 2 a nonspecific suppurative epididymitis developed, which was treated surgically, and the patient was discharged on December 5. At this time chemical examination of the blood did not reveal anything abnormal, and the general paralysis, agnosia and other focal signs had receded to the state existing prior to the development of the acute disease.

#### COMMENT

The outstanding symptoms in case 1 were rapid development of uremic symptoms, anuria, subconjunctival hemorrhages, edema, jaundice and delirium. There was evidence of rapid, progressive parenchymal destruction of the liver, as shown by a marked depression of total serum protein and its fractions and a lowering of cholesterol with almost total disappearance of the ester fraction. Primary nephritis or nephrotic syndrome is excluded by these changes occurring in a brief period and

TABLE 2—*Chemical Changes in the Blood of Two Patients Taking Pyridine as an Anticonvulsant*\*

	Date	Non protein Nitro- gen, Mg / 100 Cc	Uric Acid, Mg / 100 Cc	Total Protein, Gm / 100 Cc	Albu- min, Gm / 100 Cc	Glob- ulin, Gm / 100 Cc	Creat- inine, Mg / 100 Cc	Urea Nitro- gen, Mg / 100 Cc	Choles- terol, Mg / 100 Cc	Choles- terol Esters, Mg / 100 Cc	Phos- phorus, Mg / 100 Cc	Phos- phatase, King Units / 100 Cc	Cal- cium, Mg / 100 Cc	Chlo- rides Mg / 100 Cc	Icterus Index, Units
Patient O G (case 1)															
One month's observation in hospital															
	4/29	30.8		5.66	4.6	1.06		12.5	214	141	2.76	5.59	10.14	468	5
	5/11	32.2		6.6	5.28	1.32		12.5	192	135	2.94	3.12	9.62	470	6
	5/21	22.6		7.0	5.33	1.67		12.2	179	119	3.12	2.99	10.05	472	7
	5/27	31.2		6.25	4.8	1.45		11.3	170	121	3.2	1.7	9.7	460	7
Period of illness															
	8/25	89	1.5	1.95	3.37	1.58	7.5	101.6	1.1	Trace	5.15	6.55		100	50
	8/26	116													
	8/28	175		6.71	1.77	1.91	106	106	125	20	6.77	6.3			28
Patient W K (case 2)															
Period of illness															
	8/17	159	8.5												
	8/22	137													
	8/25	170	9.7	5.85	1.3	1.55	13		165						11
	8/26	170													
	9/7	155	4.7				5.1		166	16					
	9/18	41		5.98					178	120	3.33		9.6		15
	9/22	32	2.3				2								

\* One patient continued taking pyridine after he was observed for a month in the hospital while taking this drug. The other patient had not taken pyridine under observation previously.

# Progress in Internal Medicine

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## ALLERGY

A REVIEW OF THE LITERATURE OF 1942

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The field of allergy is being cultivated, also, it is being extended. The common allergic manifestations are hay fever, asthma and eczema, but other symptom complexes also may depend on allergy, and the list becomes longer as knowledge increases. More and more of the phenomena of allergy are being correlated with the phenomena of acute and chronic infections. Bacterial allergy is often hard to demonstrate, but nevertheless it undoubtedly plays a role in many difficult situations hard to understand without such a theory. Asthma often appears to be produced by acute colds and without other cause. One is almost forced to think of "bacterial allergy," but cutaneous tests made with various preparations of bacteria in the sputum do not give a reaction of immediate type, as might be encountered if the cause were ragweed or egg albumin—except in rare instances. Asthma, according to Landau and Gay,<sup>1</sup> has been defined by Beigel as "a multiple, functional, inflammatory bronchial stenosis." This definition might implicate the mechanisms of allergy, but it implies more the effect of a particular type of sticky exudate, as will be discussed later. When more knowledge of bacterial allergy in asthma is acquired, it may be found that the two implications go together.

The recognition that periaarteritis nodosa is encountered not uncommonly in association with severe types of asthma suggests that a lesion of the blood vessels is a part of the fundamental process. Certain local vascular disturbances may depend on allergy, as Harkavy<sup>2</sup> has shown. The Arthus phenomenon has been shown to begin with a thrombosis of small blood vessels, which leads promptly to the development of typical local necrosis.

One must consider, therefore, that lesions of the blood vessels are a part of this complex picture. The idea interferes somewhat with the earlier concept that allergy was concerned only with epithelial structures.

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1 Landau, W., and Gay, L. N. Allergy in Germany, *J. Allergy* **13** 494, 1942.

2 Harkavy, J. Vascular Allergy. Manifestations of Polyvalent Sensitization, *J. Mt. Sinai Hosp.* **8** 592, 1942.

without phosphorus retention, elevation of the blood pressure or activity of the urinary sediment

In the second case the retention of nitrogen and uric acid without elevation of phosphorus was outstanding. An inactive sediment in urine of a low specific gravity containing albumin (4 plus) speaks for an altered function of the tubules. Again a low blood level of cholesterol and generally reduced serum protein and its fractions suggest sharp depression of the function of the liver. Altered hepatic function may explain the high blood level of uric acid and the albuminuria, such as are encountered in the hepatorenal syndrome. In their discussion of the hepatorenal syndrome Orr and Helwig<sup>13</sup> concluded

There exists a close relationship between the liver and kidneys in disease since they are phylogenetically and functionally closely related. It is very probable that when the liver function breaks down in its detoxification or neutralization function that the kidneys take over the function of eliminating toxic products by excretion.

In our cases pyridine seemed to cause parenchymal damage to the liver, thus imposing on the kidneys an extra burden of eliminating toxic products in general, as well as eliminating the pyridine itself.

It has often been observed by us that when a convulsive disorder in a patient is the result of organic brain disease, such focal signs as may be evident are always increased markedly when the patient because of bromism suffers from a temporary encephalopathy. We attribute the increase of focal signs in the case reported in which there were residual signs of an astrocytoma of the brain to such a toxic encephalopathy.

#### CONCLUSIONS

Despite the relatively low toxicity of pyridine in animals, failure to find reports of toxic effects in man resulting from its administration in repeated doses of 5 to 25 minims (0.31 to 1.54 cc) and absence of any evidence of toxicity in man, when careful studies were made on 5 subjects receiving 30 to 40 minims (1.85 to 2.46 cc) of pyridine a day for periods up to a month 2 instances of later marked toxic effects were noted. In both instances the effects were those of hepatorenal disease in 1 case leading to death, in the other case followed by recovery.

Pyridine may be added to the list of chemical poisons which may produce the hepatorenal syndrome.

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13 Orr, T. G., and Helwig, F. C. The Hepatorenal Syndrome, in Frank Howard Lahey Birthday Volume, June First, Nineteen Hundred Forty, Springfield, Ill., Charles C. Thomas, Publisher, 1940, p. 339.

that guinea pigs can be bred selectively, so as to obtain a strain which is resistant to a given allergen. From this it looks as though the factor of inheritance was concerned with the capacity of the organism for the development of local tissue antibodies, but there are other possibilities. Inheritance might be concerned with the permeability of the skin and/or of the gastrointestinal tract to make the tissues more accessible to the foreign substance, or it might be concerned with the release of H substance. And then as a fourth possibility there is the ability of the organism to react to this H substance.

*Endocrine Variations*—These variations constitute another factor. So far the most promising aspect is concerned with the sex hormones in general. Pregnancy has a decided effect on hay fever and asthma, as Farmer<sup>7</sup> has outlined. One difficulty is that this effect is not always regular. Sometimes the symptoms are worse during pregnancy, but in other cases they clear entirely during the period of gestation. Emotional factors are receiving more attention. Stokes and Beerman<sup>8</sup> present a review of the problem under the title "Psychosomatic Correlations in Allergic Conditions." Jensen and Stoesser<sup>9</sup> point to the increasing recognition of emotional factors in asthma and cite cases in which the control of these factors helped greatly in the control of the asthma. Abramson<sup>10</sup> describes a woman of 31 who suffered from giant hives after swimming in cold water, when her arm was tested with ice an urticarial wheal developed at the site. At the same time she was found to be suffering from certain mental conflicts. When later these conflicts were adjusted, her sensitiveness to cold disappeared. Should one say that in her case the trouble was concerned with the quantitative development of the reaction-producing factor—the H substance, or was it concerned merely with an increased reaction to it? It is fair to anticipate that if the various factors resulting in any one response can be distinguished one from the other, the effect of emotional disturbances as well as the effect of particular endocrine variations may become more clear.

*Vitamins*—These substances are interesting to the student of the nature of allergy, but recent work tends to discredit their great importance. In 1934 Sulzberger and Simon<sup>11</sup> found that when two series

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7 Farmer, L. The Role of the Endocrines in Anaphylaxis and Allergy, *Ann Int Med* **17** 212, 1942

8 Stokes, J. H., and Beerman, H. Psychosomatic Correlations in Allergic Conditions. A Review of Problems and Literature, *Psychosom Med* **2** 439, 1940

9 Jensen, R. A., and Stoesser, A. V. Emotional Factor in Bronchial Asthma in Children, *Am J Dis Child* **62** 80 (July) 1941

10 Abramson, H. A. Editorial Comments. Physical or Psychic Allergy, *J A M A* **118** 229 (Jan 17) 1942

11 Sulzberger, M. B., and Simon, F. A. Arsphenamine Hypersensitiveness in Guinea Pigs, *J Allergy* **6** 39, 1934



for now endothelial tissues seem to be involved also. The field is extended, but with good reason.

The locality of the allergic response is another important aspect. Why does a sensitiveness to egg result in eczema in one child and asthma in another? Ragweed causes hay fever often enough, but it may produce asthma without any nasal symptoms at all, and then in rare cases it can produce a local dermatitis. Elsewhere I<sup>3</sup> have pointed out that a review of the literature on drug allergy shows that the same medicament when taken by mouth can produce asthma in one patient, a diffuse cutaneous reaction in another, or a disturbance of the blood-forming organs in a third. It would seem, therefore, that one tissue can become more sensitive than another tissue and that reactions which are localized may or may not be associated with a sensitiveness of all the tissues. Related to this idea is the observation that in certain patients seen at the very beginning of their hay fever cutaneous tests may yield quite negative results, whereas in the next year the cutaneous reactions become positive. This has been interpreted as evidence that the development of allergy in one tissue may occur before its development in other tissues. The idea explains some of the discrepancies in results of cutaneous tests, which may or may not be positive, even though the mucous membranes of the nose and the bronchi are capable of reacting so violently.

In a review of the literature of allergy of 1941 I<sup>4</sup> called attention to the advantages of separating the study of allergy as a problem in immunology from the study of asthma (and I include other allergic manifestations as well) as a problem in physiology. Since this distinction was made, the whole field is a bit clearer. Since the allergic reaction has been recognized as merely one of a variety of the causes of asthma, a considerable number of other causes have been recognized. Let us, however, discuss allergy first.

#### NATURE OF THE ALLERGIC STATE

The nature of the allergic state is still obscure, and this corner of the field needs much further cultivation.

*Inheritance*—This factor is obviously important. Jacobs and his co-workers<sup>5</sup> have confirmed the observation of Landsteiner and Chase<sup>6</sup>

3 Rackemann, F. M. Allergy, with Special Reference to Drug Allergy, New England J. Med. **224** 688, 1941.

4 Rackemann, F. M. Allergy. Review of Literature of 1941, Arch. Int. Med. **69** 128 (Jan.) 1942.

5 Jacobs, J. L., Kelley, J. J., and Sommers, S. C. Heredity, Predisposition to Sensitization in Guinea Pigs, Proc. Soc. Exper. Biol. & Med. **48** 639, 1941.

6 Landsteiner, K., and Chase, M. W. Breeding Experiments in Reference to Drug Allergy in Animals, in Proceedings of the International Congress for Microbiology, 1940, p. 772.

I believe that this observation is of considerable importance to the whole problem of food assimilation and absorption. It is interesting that the absorption of almost any food can be demonstrated if only one can find a donor who is specifically sensitive to that particular substance and whose serum has a sufficiently high reaginic titer toward it. Walzer shows that the reaction in the prepared site occurs within less than ten minutes and that it can be produced by minute quantities of the offending substance. How long the reaction will persist or how long the offending substance will remain in circulation or in the tissues has not yet been worked out. Walzer has demonstrated a method by which active sensitiveness of the tissues might occur. Meantime, Hartley<sup>16</sup> has been able to sensitize guinea pigs by single feedings of small quantities of egg albumin—and the results were better if the intestinal mucosa was injured a little by the withholding of vitamin C and the production of scurvy. Incidentally, he found that if the feeding was continued, the circulating antibodies which were demonstrable at first disappeared, and this fact helps one to understand why it is that not all persons are sensitive to all foods all the time.

The newborn babe is not sensitive. Hill and Sulzberger<sup>17</sup> showed this some years ago. And now Zohn<sup>18</sup> has tested 150 infants from 3 to 8 days of age with egg, wheat and milk and failed to obtain any positive reaction. Histamine, however, when injected in a dilution of 1:10,000, caused wheal formations consistently. Evidently the development of allergy depends on antibodies, and antibodies require time for production.

*Development of Sensitiveness from Contact*—Criepe<sup>19</sup> studied 7 pairs of identical twins, and only 3 of them behaved quite alike. In 1 pair, 1 twin had hay fever in June from grasses and the other had hay fever in August from ragweed. In another pair, the onset was at 3 and at 4 years, respectively, and finally, a sensitiveness to acetylsalicylic acid developed in 1 of a pair, whereas a sensitiveness to egg developed in the other. As Criepe says, "Contact is important, but one must explain the absence of sensitiveness to many common allergens." Just why one substance should be seized on to the exclusion of all the others is a question hard to answer. That nursing mothers can absorb undigested proteins

16 Hartley, G., Jr. The Permeability of the Gastro-Intestinal Mucosa of Guinea Pigs to Crystalline Egg-Albumin. II. Relationship Between Circulating-Antibody Titer and Severity of the Anaphylactic Shock Following the Oral Administration of Antigen to Actively Immunized Scorbutic and Non-Scorbutic Guinea Pigs, *J. Immunol.* **43** 301, 1942.

17 Hill, D. W., and Sulzberger, M. B. Evolution of Atopic Dermatitis, *Arch. Dermat. & Syph.* **32** 451 (Sept.) 1935.

18 Zohn, B. Skin Testing in the Newborn, *Arch. Pediat.* **58** 339, 1941.

19 Criepe, L. H. Allergy in Identical Twins. Report of Seven Pairs of Twins, *J. Allergy* **13** 591, 1942.

of guinea pigs were submitted to the same experimental procedure in an attempt to sensitize them to arsphenamine, the results in one series were quite different from those in the other, and they thought first of variations in vitamins in the fodder as the factor responsible for the difference. Frei<sup>12</sup> has studied this directly working especially with vitamin A (carotene), but also with the vitamin B complex and with vitamin E. Although the fodder of his animals was varied within a wide range, he could not demonstrate any significant changes in their subsequent sensitization or reaction. Feller, Roberts, Ralli and Francis<sup>13</sup> also worked on vitamin A, as well as on vitamin C. Marked and prolonged changes in the feeding of these components produced severe deficiencies, but neither these changes nor later flooding with vitamin excesses made any difference in the capacity of the animals to respond to a variety of immunologic tests. Meantime, however, Hochwald<sup>14</sup> and others have shown that the intravenous injection of ascorbic acid (vitamin C) in large quantities can protect guinea pigs against anaphylactic shock. This, however, represents the effect of ascorbic acid as a drug with its reducing action and not the effect of any vitamin lack.

*Development of Sensitiveness*—The development of sensitiveness in a susceptible animal depends on the method by which the susceptible animal is exposed. One can presume that the involvement of a particular tissue resulting in particular manifestations depends on some local injury which makes that tissue absorb the antigen a little faster than other tissues. I believe that the work of Matthew Walzei deserves more attention and recognition. He<sup>15</sup> has recently summarized a long series of studies which show that the feeding to or the injection of a foreign substance into normal subjects (whether human beings or monkeys) is followed promptly by the absorption of the substance into the blood stream and tissues. By injecting into the skin of a subject a small dose of serum from a donor who is actively sensitized Walzei can demonstrate that a local urticarial reaction appears in the prepared site within a few minutes after the foreign substance itself is fed or injected. This means that the foreign substance is absorbed unchanged or at least that its chemical subdivision has not progressed to any considerable extent.

12 Frei, W. Further Studies in Arsphenamine Hypersensitiveness in Guinea Pigs. Vitamin A (Carotene) in Relation to the Sensitization of Guinea Pigs to Old Arsphenamine, *J Invest Dermat* **5** 117, 1942.

13 Feller, A. E., Roberts, L. B., Ralli, E. P., and Francis, T. Studies on the Influence of Vitamin A and Vitamin C on Certain Immunological Reactions in Man, *J Clin Investigation* **21** 121, 1942.

14 Hochwald, A. Antiallergic Properties of Vitamin C. *Zentralbl f inn Med* **56** 769, 1935.

15 Walzei, M. Absorption of Allergens, *J Allergy* **13** 555, 1942.

quantities (0.10 cc) of the antigen every one or two weeks. In 10 of them an immediate positive reaction developed to one or another of the later doses—to the third dose in 2 patients, to the fourth in 1, to the fifth in 3, to the sixth in 1, to the seventh in 1, to the eighth in 1 and to the ninth in 1. They make the good point that the diagnostic value of tests like this diminishes with repetition. Arbesman, Witebsky and Osgood<sup>27</sup> draw similar conclusions after making tests with *Trichina* antigen on 28 consecutive patients with allergy and 91 consecutive normal persons. The incidence of positive reactions was as much as 22 per cent in the allergic group.

Two papers are concerned with the nature of the sensitizing substance. Spain, Gillson and Strauss<sup>28</sup> compared the production of sensitiveness and the subsequent reaction to extracts of serum, saliva and skin epithelium of the dog, cat and the rabbit. On the whole, a guinea pig sensitized to dog saliva reacts well to dog serum or to dog epithelium, and this fact shows that a common antigenic factor is present in the three preparations. The same thing applies to rabbit saliva, serum and epithelium. But there are certain exceptions which suggest that there may be specific factors as well and that saliva, serum and skin substance are not the same in every particular. The other paper is by Cooke,<sup>29</sup> who reviews his work on protein derivatives of common foods. In food allergy it is not usual to encounter cutaneous reactions which correspond with the history of the patient. The diagnosis is made on the basis of trial and error, as brought out by the patient's direct personal experiences. Cooke has considered that the process of digestion results in the production of intermediary substances which are the actual cause of the sensitiveness and of the symptoms. The idea is important, and Cooke has assembled a good deal of experimental work to support it.

#### HISTAMINE

In the recent review of the literature on anaphylaxis by Dragstedt<sup>30</sup> the last paragraph includes this sentence

The cardinal symptoms of anaphylaxis can thus be explained as being due, in the immediate instance, to an autointoxication by physiologically active substances normally resident in various tissue cells and liberated therefrom by some change in cellular permeability brought about by the antigen-antibody reaction

27 Arbesman, C. E., Witebsky, E., and Osgood, H. Results of Intradermal Skin Tests with *Trichina* Antigen in Allergic and Normal Individuals, *J. Allergy* **13** 583, 1942.

28 Spain, W. C., Gillson, R. E., and Strauss, M. B. Comparative Immunologic Studies with Salivary and Epithelial Extracts of the Dog, Cat and Rabbit, *J. Allergy* **13** 563, 1942.

29 Cooke, R. A. Protein Derivatives as Factors in Allergy, *Ann. Int. Med.* **16** 71, 1942.

30 Dragstedt, C. A. Anaphylaxis, *Physiol. Rev.* **21** 563, 1941.

and excrete them in their milk was shown by Donnally<sup>20</sup> in 1930. Cutaneous sites in normal persons made sensitive by intradermal injections of serum from a person sensitive to eggs would react to a tiny quantity of milk from a mother who had just eaten several eggs. In a similar experiment Brunner and Baron<sup>21</sup> illustrate the same principles for cotton seed. Also, they show that specimens of milk taken during the first two hours after the ingestion of cotton seed contain little or no antigen, but that a longer time—two and one-half to twenty-four hours—was required before the test meal gave definitely positive results. The delay in this experiment is hard to explain. Courtwright and his associates<sup>22</sup> have worked on guinea pigs sensitized by exposure to the dust of dry horse dander. This experiment was made first in 1925 by Ratner and others<sup>23</sup>. The present authors were interested particularly in the protection of their animals by histamine and histaminase. The study is mentioned here to remind the reader that sensitiveness can occur by the inhalation of dust and that in clinical practice one finds this form of sensitiveness to be much more important than any other. Cannon and his associates<sup>24</sup> produced symptoms in sensitized animals by dropping a solution of purified egg albumin into their noses. A marked pulmonary inflammation was produced in all of them, and it is interesting to have Cannon lay some stress on the development of phlebitis and thrombosis—vascular phenomena—as part of this reaction process.

The small amount of contact which is necessary to produce sensitiveness is always interesting. In 1924 Hooker<sup>25</sup> showed that 33 per cent of young subjects who had been given intracutaneous test doses of diphtheria toxin-antitoxin mixtures became skin sensitive to horse serum later. The term skin sensitive is used advisedly. The change may or may not be accompanied by the development of a general sensitiveness.

Recently, Baron and Brunner<sup>26</sup> reported much the same thing for *Trichina* antigen. Eighteen patients were given injections of small

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20 Donnally, H. H. The Question of the Elimination of Foreign Protein (Egg White) in Woman's Milk, *J Immunol* **19** 15, 1930.

21 Brunner, M., and Baron, B. The Presence of Ingested Cottonseed Protein in Woman's Milk, *J Allergy* **13** 358, 1942.

22 Courtwright, L. J., Hurwitz, S. H., and Courtwright, A. B. Inhalant Sensitization and Shock in Guinea Pigs Under Controlled Atmospheric Conditions, *J Allergy* **13** 444, 1942.

23 Ratner, B., Jackson, H. C., and Gruehl, H. L. Nasal Sensitization, Nasal Anaphylactic Shock and Respiratory Symptoms Simulating Bronchial Asthma in the Guinea Pig, *Proc Soc Exper Biol & Med* **23** 17, 1925.

24 Cannon, P. R., Walsh, T. E., and Marshall, C. E. Acute Local Anaphylactic Inflammation of the Lungs, *Am J Path* **17** 777, 1941.

25 Hooker, S. B. Human Hypersensitiveness Induced by Very Small Amounts of Horse Serum, *J Immunol* **9** 7, 1924.

26 Baron, B., and Brunner, M. Active Sensitization in Human Beings with *Trichina* Antigen, *J Allergy* **13** 459, 1942.

*Acetylcholine*—This is another substance which is normally present in the body cells and which might well be the factor released by specific reactions. It differs from histamine in some ways, but its cholinergic effect is not dissimilar. Acetylcholine itself is labile. It is destroyed by heat, it is destroyed by standing, and it disappears promptly when it is injected into the organism. On the other hand, its methyl derivative has much the same pharmacologic properties and is used rather widely in certain fields of medicine. Moll<sup>35</sup> has used it in the treatment of asthma. In doses of 10 to 20 mg given to patients with asthma mecholyl chloride (acetylbetamethylcholine hydrochloride) produced wheezing, which was usually mild but sometimes severe. In a series of nonasthmatic control subjects who received doses of the same size, symptoms referable to the chest were not observed, but general signs of parasympathetic stimulation did occur. This last observation is not surprising, because in other patients hay fever or eczema or even urticaria has been lit up in a new attack by substances other than the precise specific causative one. The experience is used by some investigators to suggest that a sort of conditioned reflex is involved in the mechanism, but better perhaps is the concept that different tissues vary in the degree of their sensitiveness. Logue and Laws<sup>36</sup> treated 11 patients suffering from chronic asthma with mecholyl chloride and found that 6, or about a half, were improved by a series of ten daily doses. Fortunately, however, 6 other patients with chronic asthma were treated in the same way and at the same time with doses of physiologic solution of sodium chloride, and 4 of these, or two-thirds, were greatly improved. Another good experiment has been spoiled by controls!

*Histaminase*—This substance is not as interesting as it appeared to be some year ago. Hawes, Alles and Miller<sup>37</sup> have repeated the original experiments of Karady and Brown, who found that anaphylactic shock in guinea pigs could be controlled by histaminase. The California investigators, however, had completely negative results. In their hands histaminase had little value. Neely<sup>38</sup> believes that allergic asthma in guinea pigs might provide a good method of measuring the effect of histaminase on the reaction. A small series of animals were treated with histaminase given in various ways during the period of sensitization and just before, as well as just after, the shock dose. No protective effect, however, was observed.

35 Moll, H. H. The Action of Parasympathetic-Mimetic Drugs in Asthma, *Quart J Med* **9** 229, 1940.

36 Logue, R. B., and Laws, C. Mecholyl (Acetyl- $\beta$ -Methyl-Choline) Desensitization, *J Allergy* **13** 414, 1942.

37 Hawes, R. C., Alles, G. A., and Miller, H. Question of Protection Against Histamine and Anaphylactic Shock in Guinea Pigs by Histaminase, *J Lab & Clin Med* **27** 337, 1942.

38 Neely, F. L. Treatment with Histaminase, *J Lab & Clin Med* **27** 319, 1941.

It is assumed that in clinical allergy in man the symptoms depend on the release from normal cells of a normal cellular constituent. In another paper from Dragstedt's laboratory, by Ojers and others,<sup>31</sup> sections of the liver were removed from dogs during anaphylactic shock and tested for their histamine content. The authors found that the amount of histamine liberated was quite enough to account for this shock symptom. Dragstedt and Silva<sup>32</sup> added trypsin to heparinized rabbit blood and found that it caused a shift in the histamine from the cells to the plasma.

*Treatment of Patients with Histamine*—This procedure is sometimes effective in allergy, but reports, past and present, are not in agreement as to the percentage of good results, and in some cases the method seems to be totally ineffective. Wells, Gray and Dragstedt<sup>33</sup> tested the method on dogs. If a real tolerance to histamine can be produced, one would expect that the secretion of acid from the dog's stomach would become less as the daily dose of histamine is continued. The authors worked with dogs the stomachs of which were prepared to produce the so-called "Heidenhain pouch." They found that when the nourishment of the dogs was good, the response to repeated doses of histamine remained quite the same even after a long series of injections. A reduction in the response occurred only in those dogs the general condition of which had suffered. The authors could not provide experimental analogy for the therapeutic effect claimed for histamine desensitization in allergy. Sheldon and his co-workers<sup>34</sup> believed that treatment with histamine might be more effective if the substance could be made antigenic by combining it with a protein, and so such preparations as histamine azocasein and a combination of histamine and azo despeciated horse serum globulin were made in the laboratory and used for the treatment of a series of patients. Good results were obtained in some cases, but, as the authors explained, there is no evidence that these results were on a specific basis or that they differed from other results produced by vaccines and other substances. The theory that histamine is the end product of a great variety of specific reactions is always attractive, but so far it is still hard to be sure of its correctness.

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31 Ojers, G., Holmes, C. A., and Dragstedt, C. A. The Relation of the Liver Histamine to Anaphylactic Shock in Dogs, *J. Pharmacol. & Exper. Therap.* **73** 33, 1941.

32 Dragstedt, C. A., and Roche e Silva, M. Effect of Trypsin upon Blood Histamine of Rabbits, *Proc. Soc. Exper. Biol. & Med.* **47** 420, 1941.

33 Wells, J. A., Gray, J. S., and Dragstedt, C. A. An Investigation of the Question of Histamine Tolerance, *J. Allergy* **13** 77, 1941.

34 Sheldon, J. M., Fall, N., Johnston, J. H., and Howes, H. A. A Clinical Study of Histamine-Azo-Protein in Allergic Disease. A Preliminary Report, *J. Allergy* **13** 18, 1941.

serum disease proper, which after all is a normal response of a normal person Toomey and Garver<sup>42</sup> present results obtained on 1,447 patients who were given cutaneous tests and ophthalmic tests just before the injection of diphtheria antitoxin Serum sickness occurred in about 30 per cent of those who had had antitoxin previously and regardless of whether the cutaneous reactions were positive, but serum sickness occurred in 48 per cent of those who showed positive ophthalmic reactions It occurred in only 23 per cent of those whose ophthalmic reactions were negative

I would emphasize that if one recalls the difference in susceptibility between three groups of patients—first, the allergic persons with histories of hay fever or asthma, second, the pretreated patients who may be actively sensitive, and, third, the normal persons with neither allergy nor previous treatment—it is quite clear that to ask one or two simple questions of the patient may bring more, useful information than any cutaneous test

*Plasma*—This substance is not quite free of reaction possibilities Polayes and Squillace<sup>43</sup> described the severe reaction with chills and shock which occurred when a woman of 29 was given 250 cc of dried normal human plasma shortly after childbirth An editorial<sup>44</sup> in *The Journal of the American Medical Association* comments on this report to say that if cutaneous tests with samples of plasma could be made, reactions would be avoided What can be done when a cutaneous test or an ophthalmic test made with a sample of the serum about to be injected (or better, with a 1:10 dilution of it in normal physiologic salt solution of sodium chloride) is found to yield a positive reaction? Glaser<sup>45</sup> finds that bovine tetanus antitoxin given to 38 children, half of whom were known to be allergic, did not cause any immediate reactions at all and produced serum disease in only about 40 per cent Top and Watson<sup>46</sup> used antitoxin which had been “despecciated” by enzymic digestion They gave this preparation to 130 patients, reactions of all kinds were greatly reduced, and certain persons who could not tolerate the usual refined or concentrated antitoxin were successfully treated with this new product Attention should be called to a recent paper by

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42 Toomey, J. A., and Garver, W. P. Sensitivity to Horse Serum Due to Previous Injections of Antigen, *Am J Dis Child* **62** 765 (Oct.) 1941

43 Polayes, S. H., and Squillace, J. A. Near Fatal Reaction to Transfusion with Dried Human Plasma Solution, *J. A. M. A.* **118** 1050 (March 28) 1942

44 Toxicity of Human Plasma, editorial, *J. A. M. A.* **120** 206 (Sept. 19) 1942

45 Glaser, J. The Use of Bovine Antitoxin for the Prophylaxis of Tetanus, *J. Pediat* **19** 403, 1941

46 Top, F. H., and Watson, E. H. Reduction of Serum Reactions, *Am J Dis Child* **62** 548 (Sept.) 1941



## SERUM DISEASE AND SERUM ACCIDENTS

In reviewing the problems of allergy in wartime Vaughan<sup>39</sup> notes that one has learned to respect the story of the patient who says he has horse asthma and so not to put him in the cavalry. One has learned that hay fever may be severe or mild, incapacitating on the one hand and only a slight nuisance on the other—and I can add that the distinction is determined by the history and clinical experience and has little to do with the size of any cutaneous reaction which might be observed. And finally the Army and Navy have learned about serum sensitiveness. Kojis<sup>40</sup> has presented a careful and complete analysis of 6,211 patients who were treated with horse serum for various reasons. He comments on the 5 patients, or just under 0.10 per cent, who died suddenly after the treatment, evidently because they were naturally sensitive to the foreign protein, they were allergic persons. Kojis describes the factors which influence the incidence of serum disease: the age and sex of the patient, the kind of serum and particularly the amount injected and the route by which it is given. He describes the many symptoms which may be included under the designation of serum disease, rashes are most common, but fever may occur by itself. Enlargement of the lymph glands, swelling of the joints, edema of the subcutaneous tissues and then, finally, various mental and nervous complications can all appear. The Arthus phenomenon with its local necrosis beginning at the site of inoculation is rare, but nevertheless it is a dramatic result which may be serious. And then finally Kojis describes the various methods by which the presence of sensitiveness to horse serum can be anticipated and by which the specific treatments which appear so necessary can be given even in the presence of this sensitiveness. It is a useful and timely paper.

In a shorter article Rackemann<sup>41</sup> calls attention to the three types of serum reactions: serious, sometimes fatal reactions in those allergic persons who never have had serum before, severe and sometimes fatal reactions in those persons who have had a preliminary dose of serum within a short time and so are actively sensitized, just like the guinea pig in the laboratory equipment (and here one can add that when more serum is given during the height of serum disease or within a few days after its subsidence, fatal reactions are particularly prone to occur), and

39 Vaughan, W. T. Problem of Allergy in Wartime, *Mil. Surgeon* **89**: 737, 1941.

40 Kojis, F. G. Serum Sickness and Anaphylaxis. Analysis of 6,211 Patients Treated with Horse Serum for Various Infections, *Am. J. Dis. Child.* **64**: 93 (July) 1942.

41 Rackemann, F. M. Medical Progress, Allergy. Serum Reactions, with Particular Reference to the Prevention and Treatment of Tetanus, *New England J. Med.* **226**: 726, 1942.

this summer a third pollen survey with observers at forty-four stations, and other communities, will, no doubt, undertake similar studies after the war. From sixty-four replies to a questionnaire on pollen sent to all members of the Society for the Study of Asthma and Allied Conditions, Vander Veer and associates<sup>51</sup> have compiled a preliminary record of the pollen which occurs in New England. It shows the pollination seasons of trees, grasses and ragweed, and it indicates the minor variations which occur from place to place. The final report should be an important addition to present knowledge. Stroh<sup>52</sup> has added a new survey of the pollen over Seattle and its vicinity, and from Brazil comes a report by Greco and others<sup>53</sup> in the state of Minas Geraes, which is on the southeastern side of Brazil and just north of Rio de Janeiro. In that state it rains from September 15 to April 15 (in the northern hemisphere these dates would be March 15 to October 15), but then the grasses come out and grow profusely until June 15 (December 15 in this hemisphere). What hay fever there is comes merely for a short time from these grasses. Phillips<sup>54</sup> has studied the pollen over South Australia.

*Chemistry of Pollen*—This factor presents an important problem difficult of solution. An excellent and a complete survey of the literature available to January 1942 has been presented by Newell<sup>55</sup>. So far it has not been possible to isolate the "skin-sensitizing principle" in pure form. In 1939 Stull and Sherman<sup>56</sup> found that extracts precipitated by half saturation with ammonium sulfate contained mostly albumin, whereas another extract precipitated by full saturation contained globulins. Both types of extract were skin-test-active,<sup>56a</sup> and both could neutralize the antibodies in the serum of ragweed-sensitive patients. Now Sherman

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51 Vander Veer, A. H., Barnard, I. M., Cunningham, T. D., Nelson, T., Pratt, H. N., and Simon, F. A. Report of the Committee on a Pollen Survey of the United States. The Society for the Study of Asthma and Allied Conditions, *J. Allergy* **13** 516, 1942.

52 Stroh, J. Flora and Pollen Surveys of Seattle and Vicinity, Northwest Med **39** 258, 1940.

53 Greco, J. B., Lima, A. O., and Tupinamba, A. The Pollen Content of the Air in Belo Horizonte, Brazil, *J. Allergy* **13** 411, 1942.

54 Phillips, M. E. Studies in Atmospheric Pollen, *M. J. Australia* **2** 189, 1942.

55 Newell, J. M. A Review of Chemical Studies on the Allergens in Pollens, *J. Allergy* **13** 177, 1942.

56 Stull, A., and Sherman, W. B. Further Studies on the Allergenic Activity of Protein and Nonprotein Nitrogen Fractions of Ragweed Pollen Extract, *J. Allergy* **10** 130, 1939.

56a "Skin-test-active" means capable of eliciting a positive cutaneous reaction in a patient already sensitized.

Simon<sup>47</sup> which brings out two interesting points Simon finds that hypersensitiveness to mammalian serum is only in part species specific The serum of some sensitive persons will neutralize the antibodies (reagins) for many other mammalian serums, but the serum of others will neutralize the antibodies only for itself and perhaps for one or two other mammals The possibility that among the larger land mammals is an antigenic factor which is common—a group-specific antigen, as well as the more typical species-specific antigen—is suggested Simon points out that different human beings react to the same serum complex differently, just as Landsteiner could show that of two chemicals applied to the human skin, certain persons will become sensitive to one, others to the second and some to both The other suggestion—that the so-called “natural” sensitiveness to horse serum which is sometimes observed in persons who give no history of previous contact with the substance may depend on the common group-specific antigen derived perhaps from eating meat of various kinds—is attractive

Reactions to tetanus toxoid have been greatly reduced by improvements in the method of preparing the material The details are described in Rackemann's article already mentioned<sup>41</sup> Peshkin<sup>48</sup> treated 65 children known to be allergic to various substances with the combined alum-precipitated diphtheria and tetanus toxoids Local reactions occurred in 25 per cent, but constitutional reactions were not observed The antitoxin titer rose to satisfactory levels Incidentally, the following report is of interest Zuger, Greenwald and Gerber,<sup>49</sup> of the New York Department of Health, treated two groups of guinea pigs, 75 in each, with two doses of alum-precipitated tetanus toxoid and then inoculated the animals with tetanus spores In the group which received an additional booster dose of toxoid at the time of inoculation, 8 animals had local tetanus, and none died In the other group, however, without the booster dose, 13 animals had local tetanus and 4 had generalized tetanus

#### HAY FEVER

*Pollen Surveys*—These surveys, including daily pollen counts, are exciting the interest of persons who would like to get rid of all pollen-producing plants by pulling them up The state of Michigan<sup>50</sup> began

47 Simon, F A Human Allergy to Mammalian Sera, J Exper Med **75** 315, 1942

48 Peshkin, M M Immunity to Tetanus Induced by Combined Alum-Precipitated Diphtheria and Tetanus Toxoids, Am J Dis Child **62** 309 (Aug) 1941

49 Zuger, B, Greenwald, C K, and Gerber, H Tetanus Immunization Effectiveness of the Stimulating Dose of Toxoid Under Conditions of Infection, J Immunol **44** 309, 1942

50 Ragweed Pollen Count, Medical News (Michigan), J A M A **119** 959 (July 18) 1942

and consists of a polypeptide carrying a large percentage of basic amino acid. Treatment with this material gave good results in a moderate number of cases.

Taub and Rubens<sup>63</sup> made an aqueous solution of ragweed which was frozen and dried *in vacuo* and then taken up in sesame oil with the idea that absorption would be slow and the effect more prolonged. So far, the authors have not found any reports of sensitizations to sesame oil, and the preparation seems to keep well, remaining unchanged for over a year. However, I am not too enthusiastic about oily preparations.

*Treatment of Hay Fever*—This has not been advanced much. The mechanism of the good results remains obscure, and the only real fact is that each year an ever increasing number of patients apply to clinics for treatment and that a certain proportion of these patients report at the end of the season that they have been much more comfortable than usual. The technic of treatment varies widely in different clinics. Golan, Hill and Sack<sup>64</sup> compare the effects of preseasonal and coseasonal treatment, on the one hand, and preseasonal treatment alone, on the other. The results were substantially the same in the two groups, and they conclude that little was to be gained by continuing the specific therapy during the pollen season. Markow and Rosen,<sup>65</sup> on the other hand, had better results with perennial than with preseasonal methods. Stoesser,<sup>66</sup> of the University of Minnesota, has analyzed his results and declares that long preseasonal or perennial therapy is the best.

The study of oral therapy with pollen has been continued. Iliff and Gay<sup>67</sup> present a table of all the results previously reported in the literature, commenting on their wide divergence. When ragweed pollen was given in large repeated doses (500 to 250,000 Noon units, or 0.50 to 250.0 mg.) before the season, the results were not nearly so good as those in another series of patients who were treated by the conventional hypodermic method. The results were good in only 13 of 62 patients treated by oral doses before the season, and in none of the 20 patients treated during the season were there any good results at all. Furthermore, abdominal pain, nausea and other reactions were encountered. Of the group of 37 patients treated by hypodermic injection in the same

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63 Taub, S. J., and Rubens, E. A Preliminary Report on the New Slowly Absorbed Medium for Use in Hay Fever Treatment, *J. Allergy* **13** 138, 1942.

64 Golan, H. G., Hill, R., and Sack, S. S. The Value of Continuing Preseasonal Therapy During the Pollen Season, *J. Allergy* **13** 300, 1942.

65 Markow, H., and Rosen, E. A. Comparison of Results of Preseasonal and Perennial Methods of Treatment of Ragweed Hay Fever, *M. Rec.* **155**:203, 1942.

66 Stoesser, A. V. Recent Observations on Hay Fever in Children, *Journal-Lancet* **62** 174, 1942.

67 Iliff, E. H., and Gay, L. N. Oral Treatment with Ragweed Pollen, *Bull. Johns Hopkins Hosp.* **70** 378, 1942.

and Hebard<sup>57</sup> find that constitutional reactions following treatment are more likely to occur in those patients who give strong cutaneous reactions to the globulin fraction, with or without reaction to albumin at the same time. Treatment of this group is difficult, but it can be successful if the pollen doses are regulated with care. They have to be kept small in most cases. Stull, Sherman and Wing<sup>58</sup> find that extracts prepared with water or with solutions of sodium bicarbonate or sodium hydroxide behaved differently as far as cutaneous tests and neutralization tests were concerned. It is evident that different methods of extraction produce materials which have slightly different reactions.

Roth and Nelson<sup>59</sup> find two protein fractions in ragweed pollen. One is of large molecular size and is responsible for the precipitin reaction with rabbit antiserum. The fraction of small molecular size produces the cutaneous reaction in human subjects. When a sample of pollen was extracted repeatedly with water, the later extracts no longer produced a cutaneous reaction, but the residue was still high in its nitrogen content and potent in its ability to produce immune reactions. Abramson and his co-workers<sup>60</sup> have studied pollen by electrophoresis. When a small current of electricity is passed through a solution of proteins those elements which are negatively charged go in one direction and those which are positively charged in another. Ragweed contains a major component which is negatively charged, is colorless, produces extensive cutaneous reactions and causes symptoms. It migrates slowly. Of less importance is a smaller molecule which is pigmented and moves rapidly toward the negative pole. It carries a positive charge. The difficulty is that this also is a skin-sensitizing substance.

In a paper to be published Newell<sup>61</sup> demonstrates, first, that the components separated by electrophoresis are not pure and, second, that each of them studied so far gives a cutaneous reaction test to greater or less extent. Rockwell<sup>62</sup> describes a preparation of ragweed pollen which can be precipitated by hydrochloric acid which he claims is pure.

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57 Sherman, W. A., and Hebard, S. A Method of Determining the Probability of Constitutional Reactions During Treatment of the Ragweed Hay Fever Patient, *Am J M Sc* **203** 383, 1942.

58 Stull, A., Sherman, W. B., and Wing, W. M. Antigenic Fractions in Ragweed Pollen, *J Allergy* **13** 537, 1942.

59 Roth, R. R., and Nelson, T. Proteins of Ragweed Pollen, *J Allergy* **13** 283, 1942.

60 Abramson, H. A., Moore, D. H., and Gettner, H. H. Electrophoretic and Ultracentrifugal Analysis of Hay-Fever-Producing Component of Ragweed Pollen Extract, *J Phys Chem* **46** 192, 1942.

61 Newell, J. M. Electrophoretic Studies on the Chemical Fractionation of Ragweed Pollen Extracts, to be published.

62 Rockwell, G. E. Studies on Chemical Nature and Standardization of Pollen-Antigen, *J Immunol* **43** 259, 1942.

Chicago Morrow, Lowe and Prince<sup>72</sup> have collaborated in a study of the molds recovered in various parts of central and southwestern United States. Certain molds, like *Aspergillus* and *Penicillium*, occur everywhere and are present at almost all times of the year, including the northern stations during cold weather. Other molds, however, like *Alternaria* and *Homodendrum*, have a more definite seasonal fluctuation. The individual seasons, however, vary considerably from year to year, and the molds vary much more than do the pollens. In Texas the curves of the mold counts are rather flat, whereas in the northern area sharp peaks occur, evidently dependent on changes in wind currents, weather and dampness. It is interesting that on one occasion molds were recovered from the air immediately after a heavy fall of snow and several days of near zero weather. Bernstein and Feinberg<sup>73</sup> have also studied the molds in the Chicago air and for a total period of five years. They agree that individual fungi vary widely in their relation to seasons and weather, the incidence of some having relatively little relation to the time of year. It begins to look as though molds were of even greater importance than has been appreciated.

I would like to go back to an observation which was made by Rackemann, Randolph and Guba<sup>74</sup> in 1938 that in the case of the mold *Cladosporium* a well marked species specificity was clearly demonstrated in a small group of patients. Since then cutaneous tests with the products of stock mold cultures have been made in many clinics and with results which are not always clearcut and distinct. The results are suggestive rather than clearly positive. I wonder whether this observation may not be important after all, that a much higher degree of specificity exists among the molds than has been so far appreciated. On the other hand, I and many others have tested patients not only with a single strain of *Alternaria*, for example, but with a number of stock strains at the same time and yet have not encountered variations in the reactions which might be called striking. The concept of a high degree of specificity is interesting, but so far at least it cannot be demonstrated in any number of patients. The whole problem concerning the importance of fungi in allergy of the respiratory tract needs further study. Waldbott and his assistants<sup>75</sup> found that cutaneous reactions to molds

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72 Morrow, M. B., Lowe, E. P., and Prince, H. E. Mold Fungi in Etiology of Respiratory Allergic Diseases. Survey of Air Borne Molds, *J. Allergy* **13**, 215, 1942.

73 Bernstein, T. B., and Feinberg, S. M. Air-Borne Fungus Spores. Five Year Survey of Daily Mold Spore Content of Chicago Air, *J. Allergy* **13**, 231, 1942.

74 Rackemann, F. M., Randolph, T. G., and Guba, E. F. The Specificity of Fungous Allergy, *J. Allergy* **9**, 447, 1938.

75 Waldbott, G. L., Blair, K. E., and Ackley, A. B. An Evaluation on the Importance of Fungi in Respiratory Allergy, *J. Lab. & Clin. Med.* **26**, 1593, 1941.

season, good results were obtained in 24. The oral treatment cannot compare with the subcutaneous method. As for "coli metabolin" (filtrate of *Escherichia coli* [Tosse]), Loveless and Baldwin<sup>68</sup> studied it carefully but found that "the transient benefits were duplicated in degree and duration by injections of saline." Meantime, the treatment of hay fever is not a simple or casual procedure to be undertaken without proper consideration. Francis<sup>69</sup> took care of a young married woman who suffered a severe general reaction after an injection of grass pollen which resulted in an abortion of her pregnancy. Colmes<sup>70</sup> has followed a number of patients who gave histories quite typical of ragweed hay fever but in whom cutaneous tests were always negative. Ophthalmic tests, however, yielded positive reactions in many of them, and the results of nasal tests made by the insufflation of dry pollen were positive in several. Treatment was given in large doses, and good results were obtained in over half the patients. Meantime, it is interesting that general constitutional reactions of slight degree were observed in 5 patients. Here is another illustration of the discrepancies which are observed frequently. Even though the cutaneous reaction is slight, the occurrence of constitutional reaction shows that the patient is sensitive nevertheless.

Hay fever is the typical form of allergic manifestation. It is a common disease. It seems almost pathetic that one knows so little about its mechanism and especially about the method by which the good results in treatment are obtained. One feature is impressive: that the gross results reported from those clinics which treat a large number of patients show about the same percentage figures. These results are excellent in about 20 per cent of cases, they are good in another 60 per cent, and they are poor in about 20 per cent, and this despite the fact that different pollen material, different kinds of extract and different techniques of treatment are employed. The field is open, and if this portion of it can be cultivated, the harvest will be abundant.

*Fungus Spores*—These can also cause hay fever. During the last year several excellent papers have been presented. Durham<sup>71</sup> gives an excellent scholarly bibliography with a historical survey of the whole mold problem, including a five year survey of the mold *Aspergillus* in

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68 Loveless, M. H., and Baldwin, H. S. "Coli Metabolin" Therapy in Hay Fever. Psychogenic Benefits, *J. A. M. A.* **118** 451 (Feb. 7) 1942.

69 Francis, N. Abortion After Grass Pollen Injection, *J. Allergy* **12** 559, 1941.

70 Colmes, A. Pollen Disease in the Absence of Positive Skin Tests, *New England J. Med.* **225** 817, 1941.

71 Durham, O. C. Air-Borne Fungus Spores as Allergens, Publication 17, American Association for the Advancement of Science, New York, Doubleday, Doran & Company, 1942, vol. 32.

hard to prove except in a few isolated cases. The bronchial spasm could be a conditioned reflex from some disturbance of the nose and sinuses, but this idea is likewise hard to demonstrate except in a few particular cases. Nervous factors are present, but whether they are the cause of the process or merely the result of it is hard to say. Finally come the theories concerning endocrine substances and vitamins, which so far are only suggestions. Here is another problem, another portion of the field which is wide open and full of stones.

*True Pathologic Causes of Asthma*—This type of cause is being recognized more and more—as suggested in the opening paragraphs of this review. This is not the place for any analysis of the large literature, but attention can be called to certain papers. Carcinoma can involve any portion of the lung, and the symptoms will vary in accordance with its location, particularly if the wall of the bronchus is involved. A paper by Holmes<sup>78</sup> contains two schematic diagrams which give the whole story in a clear and simple manner. Prickman and his associates<sup>79</sup> describe 3 patients who complained primarily of asthma but whose wheezing was due to carcinoma of the bronchus. Nofsinger and Vinson<sup>80</sup> had a patient whose cough and wheeze seemed to originate on the right side of his thorax. He had no pain, and he did not expectorate blood, but what he had was an intrabronchial metastasis of hypernephroma. The literature on cancer of the lung is reviewed by Perrone and Levinson<sup>81</sup> in a helpful article. In bronchiectasis the sputum is thin and watery, it is not often viscid and tenacious. Patients with this condition complain of cough, and occasionally they wheeze. In asthma, however, the sputum does not flow freely. It is tenacious and is highly viscid. Patients with asthma wheeze, and occasionally they cough. It is interesting to consider that the difference between the two groups depends chiefly on the physical characteristics of the bronchial exudate. The natural history of bronchiectasis is described in a scholarly paper by Ogilvie<sup>82</sup>. Pulmonary fibrosis may cause increasing dyspnea. In 2 cases described by Linenthal<sup>83</sup> autopsy revealed changes in small blood

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78 Holmes, G. W. Carcinoma of the Bronchus, *New England J. Med.* **227**: 503, 1942.

79 Prickman, L. E., Maytum, C. K., and Moersch, H. J. Asthma and Primary Carcinoma of Bronchus, *J. Allergy* **13** 261, 1942.

80 Nofsinger, C. D., and Vinson, P. P. Intrabronchial Metastasis of Hypernephroma Simulating Primary Bronchial Carcinoma, *J. A. M. A.* **119** 944 (July 18) 1942.

81 Perrone, J. A., and Levinson, J. P. Primary Carcinoma of the Lung (Report of One Hundred and Fifteen Cases, Thirty-Eight Autopsies and Seventy-Seven Bronchoscopic Biopsies), *Ann. Int. Med.* **17** 12, 1942.

82 Ogilvie, A. G. The Natural History of Bronchiectasis, *Arch. Int. Med.* **68**, 395 (Sept.) 1941.

83 Linenthal, H. Observations Concerning Pulmonary Fibrosis in Raynaud's Disease, *J. M. Soc. New Jersey* **227** 433, 1942.



were positive in 69 per cent of a large group (841) of allergic patients. But in spite of this they confess that allergy of the respiratory tract due to one single fungus is rare, and it would seem likely that their observations are based on cutaneous reactions which are not as clearcut and sharp as one would like to see. Perhaps the technic of making extracts is faulty. Pratt,<sup>76</sup> for example, finds that when the spores and the mycelial threads of *Alternaria* were each obtained in a relatively pure state, cutaneous tests made with spore extracts gave a much greater reaction than did the tests with mycelial extracts. Crossed experiment showed that spore extracts could sensitize to mycelial extracts, but per contra mycelial extracts had no effect on sensitiveness to spores.

#### ASTHMA

Last winter at the meeting of the American Society for the Study of Asthma and Allied Conditions, Dr T B Mallory showed a chart illustrating the mode of death of 50 patients suffering with severe asthma who had come to autopsy at the Massachusetts General Hospital. Each patient was represented by a horizontal line which began at the age of onset and ended at the age of death. The chart as a whole demonstrated three points. First, when asthma begins in childhood and before the age of 20, life runs its usual course, and death occurs some time after the age of 50 and is caused ordinarily by pneumonia or by heart disease, at least it is not due to asthma. Second, when asthma begins in early middle age, between the ages of 30 and 40, it may be complicated by periarteritis nodosa, and on the chart were represented 5 patients with this disease, which makes the rather high incidence of 10 per cent for periarteritis nodosa in severe asthma. Third, the chart showed that when asthma begins late in life, after the age of 45, the course of the disease may be short and death may occur from asthma within as little as two or three years after the onset. Does this mean that every patient in whom asthma begins after the age of 45 is doomed to die soon? It is this study of the pathologic aspects which has led to a careful follow-up of end results, which will be analyzed and published in the future.

I am convinced that "intrinsic asthma" is a special type of asthma which has nothing to do with allergy in the ordinary sense. Attempts to associate the disease with contact with any particular dust or food substance are quite unavailing. The clinical history of patients with this type of asthma cannot be explained in any such easy fashion. Bacterial asthma it might be—dependent on a hypersensitiveness to the products of bacterial action in some form of infection. This again is

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<sup>76</sup> Pratt, H N. The Comparative Atopic Activity of *Alternaria* Spores and Mycelium, *J Allergy* **13** 227, 1942.

<sup>77</sup> Rackemann, F M. Intrinsic Asthma. Further Observations, *J Allergy* **13** 622, 1942.

Other points are of less importance. Maisel and Somkin<sup>89</sup> have added nicotinic acid (niacin) in doses of 0.10 Gm to the list of those substances which can relieve asthma by intravenous injection. Variations in the potassium intake have been described as important in asthma, but Harsh and Donovan<sup>90</sup> studied the problem and could find no relation between the severity of the symptoms and diets containing as little as 1 Gm of potassium chloride per day or as much as 18 Gm per day. Racemic epinephrine is a mixture of equal parts of levorotatory and dextrorotatory substances, according to a report of the Council on Pharmacy and Chemistry of the American Medical Association.<sup>91</sup> Epinephrine U. S. P. is levorotatory and is active, dextrorotatory epinephrine is, however, inactive, so that racemic epinephrine is only half as strong as the conventional product. A true sensitiveness to epinephrine has been described by Dumm,<sup>92</sup> who observed acute urticaria in a patient with asthma after an injection of 0.75 cc of 1:100 solution of epinephrine hydrochloride. Finally, Vaughan and Graham<sup>93</sup> warn one again concerning the use of morphine in the treatment of asthma. There are two reasons which deserve repetition here. First, morphine depresses the respiratory center and under the influence of the drug the patient may be literally suffocated by the viscid secretion that fills all of his tubes. Secondly, morphine is a parasympathomimetic drug. A solution of morphine will produce a cutaneous reaction on the arm of a normal person. Morphine can actually cause bronchospasm and so may be the last straw which kills the patient. "After the injection he went to sleep and slept until some one realized that he wasn't breathing any more!"

#### ECZEMA

The nature of eczema, and particularly the differences between the so-called "atopic eczema" and the so-called "contact dermatitis," are discussed in two excellent articles by Hill.<sup>94</sup> In his practice among infants and young children he encountered and studied 105 cases of

89 Maisel, F. E., and Somkin, E. Treatment of Asthmatic Paroxysm with Nicotinic Acid, *J. Allergy* **13** 397, 1942.

90 Harsh, G. F., and Donovan, P. B. The Effect of Wide Variations in Potassium-Sodium Intake in Asthmatic Children, *J. Allergy* **13** 105, 1942.

91 Status of Racemic Epinephrine for Oral Inhalation, report of the Council on Pharmacy and Chemistry, *J. A. M. A.* **120** 287 (Sept. 26) 1942.

92 Dumm, J. F. Urticarial Reactions in an Asthmatic Patient Following an Injection of Natural Epinephrine, *Prensa med. argent.* **28** 303, 1941.

93 Vaughan, W. T., and Graham, W. R. Death from Asthma. A Warning, *J. A. M. A.* **119** 556 (June 13) 1942.

94 Hill, L. W. (a) The Classification of Eczematoid Eruptions in Children with Especial Reference to Contact Dermatitis, *J. Pediat.* **20** 537, 1942, (b) The Production of Nonetiological Skin Hypersensitivity to Foods by Natural Means in Atopic Persons, *J. Allergy* **13** 366, 1942.

vessels, and one wonders whether these can be related to the other changes observed in periarteritis nodosa. And then finally emphysema may itself cause asthma, a wheeze which complicates the ever increasing dyspnea. This is the common type of "pulmonary insufficiency," a process which makes the lungs as a pair of bellows inefficient and unable to carry on their normal function. "The Vanishing Lung" is the interesting title which Allison<sup>84</sup> uses to describe the insidious slow increase of the destruction of the structure and the function of the lung. Emphysema occurs in all cases of asthma as a temporary stretching of the lung, physiologic emphysema which disappears when the attack subsides. In organic emphysema the lesion is permanent, it is irreversible. Also, the symptom is persistent and unfortunately irreversible. Meanwhile, Traisman<sup>85</sup> describes death from asthma in an infant aged 12 months. Autopsy showed marked emphysema, but the mucus plugs which are so characteristic of fatal asthma in adults were encountered in only two of the bronchi.

*Treatment of Asthma*—On this subject there is nothing really new. Gay and Reinhoff<sup>86</sup> have published the results of bilateral resection of the pulmonary plexus of the vagus nerve. The operation is radical and dangerous, since 6 of the 21 patients died within a week. In 8 of the 21, however, the results were quite successful. Three patients have been restored to almost perfect health, and 5 others are so relieved that they can resume gainful occupations. Potassium iodide, whether given by vein or by mouth, can be demonstrated in the bronchial secretion within fifteen minutes, according to Tuft and Levin<sup>87</sup>. It is excreted by the mucoid cells in the bronchial tree, and it has two actions, the first is to stimulate the smooth muscle of the bronchi, helping them to move the secretion, and the second is to liquefy the secretion and make it less viscid. No wonder potassium iodide is so effective!

Bases and Kurtin<sup>88</sup> find that 6 of 7 patients who died in an attack of asthma were actually suffocated by the secretion in the bronchi, and they suggest that bronchoscopy to remove the block may be life saving. In 1 of their patients bronchoscopy resulted in immediate improvement. It is a timely suggestion.

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84 Allison, S. T. The Vanishing Lung. Report of a Case of Advanced Bullous Emphysema, *Ann Int Med* **17** 139, 1942.

85 Traisman, A. S. The Pathology of Asthma in Children, *Arch Pediat* **58** 407, 1941.

86 Gay, L. N., and Reinhoff, W. M. Treatment of Intractable Bronchial Asthma by Bilateral Resection of Pulmonary Plexus. Further Observations, *Bull Johns Hopkins Hosp* **80** 386, 1942.

87 Tuft, L., and Levin, N. Studies in Expectorant Iodides, *Am J M Sc* **203** 717, 1942.

88 Bases, L., and Kurtin, A. Prevention of Death in Status Asthmaticus. Value of Bronchoscopy, *Arch Otolaryng* **36** 79 (July) 1942.

important, is the list of substances occurring in cosmetics and drugs. It is said that 90 per cent of the dermatitis which occurs on the eyelids is caused by nail polish. Nine new cases are described by Palmer<sup>100</sup>. Burgess<sup>101</sup> reports that the active ingredient in nail polish is the basic lacquer made of nitrocellulose but that occasional reactions depend on the coloring matter. Butesin picrate is an old offender, but Boylan<sup>102</sup> reports a new case of extensive dermatitis which complicated a bad burn that was treated with this drug. In a case reported by Laval<sup>103</sup> a patient was treated with a solution of paredrine hydrobromide (p-hydroxy- $\alpha$ -methyl-phenylethylamine hydrobromide) dropped into the eye daily for seventy-nine days. On the eightieth day the concentration was increased from 1 to 3 per cent, and three days later typical conjunctivitis with surrounding dermatitis developed. Bernreiter<sup>104</sup> obtained a positive patch reaction with a 1:5 dilution of sodium hypochlorite in a woman in whom vaginitis developed after she had used a douche which contained sodium hypochlorite (clorox).

*Drug Allergy*—This subject also includes a variety of general disturbances. Fox, Gold and Leon<sup>105</sup> describe a severe reaction with fever, flushing, erythema, salivation, nausea and vomiting which followed an intravenous injection of mercupurin into a woman of 27. Phenobarbital caused an exfoliative dermatitis which was fatal in the case reported by Winer and Baer<sup>106</sup>. Kampmeier<sup>107</sup> describes a patient in whom a generalized urticaria developed on each of four attempts to inject tryparsamide into a vein. This led to the practical finding that at Vanderbilt University Hospital 829 patients had been given 43,308 injections of tryparsamide but that urticaria followed in only 5 instances. In none of them did the reaction occur before the ninth dose.

Goldburgh and Baer<sup>108</sup> report the ninth death recorded in the American literature after intravenous administration of diodrast. Do

100 Palmer, R. B. Dermatitis from Nail Lacquer, *Arch. Dermat. & Syph.* **44** 13 (July) 1941.

101 Burgess, J. F. Nail Polish Dermatitis, *Canad. M. A. J.* **45** 336, 1941.

102 Boylan, C. E. Butesin Picrate Dermatitis with Case Report, *Illinois M. J.* **79** 226, 1941.

103 Laval, J. Allergic Dermatitis and Conjunctivitis from Paredrine Hydrobromide, *Arch. Ophth.* **26** 585 (Oct.) 1941.

104 Bernreiter, M. Sodium Hypochlorite Dermatitis, *J. Kansas M. Soc.* **42** 424, 1941.

105 Fox, T. T., Gold, H., and Leon, J. Hypersensitiveness to A Mercurial Diuretic with Observations on Its Mechanism, *J. A. M. A.* **119** 1497 (Aug. 29) 1942.

106 Winer, N. J., and Baer, R. L. Exfoliative Dermatitis Due to Phenobarbital, *Arch. Dermat. & Syph.* **43** 473 (March) 1941.

107 Kampmeier, R. H. Urticaria Due to Tryparsamide, *Arch. Dermat. & Syph.* **44** 671 (Oct.) 1941.

108 Goldburgh, H. L., and Baer, S. Death Following the Intravenous Administration of Diodrast, *J. A. M. A.* **118** 1051 (March 28) 1942.

atopic eczema and 31 cases of contact dermatitis. Mixtures of the two types are common and present difficult problems. Also, the presence of eczema makes the skin more susceptible to noxious agents of all sorts, particularly to soap and water. Hill's discussions reflect his wisdom, experience and common sense.

Another good paper is by Osborne, Jordan and Hallett<sup>95</sup> who reviewed 120 cases of eczema, finding that foods played a part in not over 10 to 15 per cent. It is interesting to find that factors of dust in the environment, wool, silk, feathers, animal danders, etc., were causes of eczema in the large majority of cases. This is interesting if only because it suggests that absorption through the respiratory tract is quite as important as absorption through the gastrointestinal tract. The observation is correct, but what is the mechanism of this absorption? Can proteins pass through the bronchial or the alveolar epithelium? The questions are proper. In adults dermatitis of the contact type is the important form of eczema. Oliver<sup>96</sup> gives a list of causes met with in industry, as recorded for the United States Public Health Service. They include the following ones: petroleum oil and greases, alkalis, including cement and concrete—producing the so-called "cement itch", solvents, chromic acid and its salts, metals and plating, dyes, plants, rubber and its compounds, paints and varnishes, and, finally, synthetic resins. The list is long and no doubt will be still longer later. Lane and his co-workers<sup>97</sup> are also interested in industrial and occupational dermatoses and have done much to stimulate interest in this subject. Lane<sup>98</sup> says that a conservative estimate for the country as a whole is about 25,000 new cases of industrial dermatitis a year and that in some industries the development of dermatitis constitutes a serious problem. Meantime, soap is an aggravating factor. At the meeting of the American Medical Association at Atlantic City, N. J., in June 1942, Drs. Lane and Blank<sup>99</sup> presented an exhibit of cutaneous detergents—"Soap substitutes of various kinds which are useful in the treatment of contact dermatitis when soap itself cannot be used." The important points of this exhibit have been published recently. Next in importance to the list of foreign substances met with in industry, and perhaps even more

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95 Osborne, E. D., Jordan, J. W., and Hallett, J. J. The Practical Management of Eczema in Infants and Children, *New York State J. Med.* **42** 47, 1942.

96 Oliver, E. A. Contact Dermatitis, *N. Clin. North America* **26** 13, 1942.

97 Lane, C. G., Denmie, C. C., Downing, J. G., Foerster, H., Oliver, E. A., and Sulzberger, M. Industrial Dermatoses. A Report by the Committee on Industrial Dermatoses of the Section on Dermatology and Syphilology of the American Medical Association, *J. A. M. A.* **118** 613 (Feb. 21) 1942.

98 Lane, C. G. The Recognition of Occupational Dermatoses, *New England J. Med.* **39** 42, 1942.

99 Lane, C. G., and Blank, I. H. Cutaneous Detergents, *J. A. M. A.* **118** 804 (March 7) 1942.

generalized macular eruptions appeared. Thrombopenic purpura followed medication with sulfathiazole in the case reported by Rosenfeld and Feldman<sup>111</sup>. Rothstein and Cohn<sup>112</sup> had an analogous experience. Acute hemolytic anemia and toxic hepatitis with evidence of damage both to the liver and to the kidneys developed in their patient after treatment with sulfathiazole. The man was extremely ill, but he recovered. Not always, however, does sulfathiazole act on the blood-forming organs. In the 3 cases reported by Denmie<sup>113</sup> pustular and vesicular lesions developed on the hands and feet and later over the whole body. In 1 patient the relation between the lesions and the drug was not recognized at first, and when treatment was continued, swelling of the tongue, with closure of the eyes, developed, and for a time the patient's condition was serious. As Nelson<sup>114</sup> says, the first course of treatment with a sulfonamide preparation is not apt to lead to complications, but if an interval is allowed to lapse, particularly if this interval is only a few weeks or a month in duration, and then the drug is given again, a reaction typical of allergy may occur. Sulfadiazine (2-[para-aminobenzenesulfonamido]-pyrimidine) may also cause reaction. In the case reported by Curry<sup>115</sup> acute agranulocytosis developed in a woman of 41 after prolonged administration of sulfadiazine. What interests me is that this reaction may involve quite different organs in different patients. Keefer<sup>116</sup> also lays stress on this in his excellent review of all the toxic reactions which may follow treatment with a sulfonamide compound. The paper includes a classified bibliography which should be helpful to those persons interested in the subject. In some cases the reaction can be called toxic because it appears on the first dose in a patient who has never had previous contact with the substance. But where there is a story of previous treatment without ill effects and then of an interval before the second course, one has to believe that this first treatment produced a change in the patient to

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111 Rosenfeld, S., and Feldman, F. Thrombopenic Purpura Due to Sulfathiazole, *J A M A* **118** 974 (March 21) 1942

112 Rothstein, I., and Cohn, S. Acute Hemolytic Anemia Autoagglutination Toxic Hepatitis and Renal Drainage Following Sulfathiazole Therapy, Case Report, *Ann Int Med* **16** 152, 1942

113 Denmie, C. D. Angioneurotic Edema and Dermatitis Venenata-Like Lesions Due to the Oral Administration of Sulfathiazole, *J A M A* **120** 197 (Sept 19) 1942

114 Nelson, J. Acquired Sensitivity to Sulfonamide Drugs, *J A M A* **119** 560 (June 13) 1942

115 Curry, J. J. Acute Agranulocytosis Following Sulfadiazine, *J A M A* **119** 1502 (Aug 29) 1942

116 Keefer, C. S. Toxic Reactions Following Sulphonamide Treatment, *New England J Med* **226** 266, 1942

these dreadful experiences mean that intravenous pyelography with diodrast should be abandoned? Far from it! The subject was discussed at a recent meeting of the American Roentgen Ray Society, and it was reported that among 600,000 patients studied by intravenous pyelography with the use of many radiopaque preparations, including diodrast, only 25 deaths had occurred. On the other hand, constitutional reactions, sometimes only a chilly sensation with headache, other times a severe collapse with chills, weakness and impalpable pulse, occur with considerable frequency. Naterman and Robins<sup>109</sup> found that cutaneous tests made by injecting 0.05 cc. of undiluted diodrast into the skin of the forearm gave positive results in 155 of 404 patients. When the drug was given regardless of the result of the test (as it had been given in times past), reactions occurred in 67 patients, or 43 per cent. It is interesting, however, that in the others no reactions occurred, even though the result of the test was positive. The cutaneous test yielded a negative result in 249 of the 404 patients, but nevertheless reactions did occur—in 14 instances. The result of the cutaneous test evidently has a considerable significance, but on the other hand, the test is not infallible. I believe that whenever a foreign substance of complex nature, be it drug or serum, is to be injected into a patient, two simple questions should be asked. The first is "Are you allergic?" (which means Does this patient have hay fever or asthma or some other manifestation of allergy which indicates that he is likely to have a capacity for the development of sensitiveness to foreign substances?) The second question is "Have you ever had an injection of this substance before?" (which means Has he had previous treatment which might have sensitized him?) Naterman and Robins found a positive history of allergy in 38, or 9 per cent, of their patients, and 31, or 80 per cent, of these showed positive cutaneous reactions. Unfortunately, the authors do not tell about the relation between the clinical history of allergy and the occurrence of systemic reactions to diodrast.

Reports on reactions to sulfonamide drugs are numerous. Four interesting papers are concerned with reactions to sulfathiazole (2-[paraaminobenzenesulfonamido]-thiazole). Sams and Capland<sup>110</sup> describe a patient in whom an eczematous dermatitis of the external ear developed after local treatments with sulfathiazole powder. Treatment was omitted, but several weeks later the same man was given 15 grains (0.97 Gm.) of sulfathiazole by mouth. Within four hours an acute dermatitis with massive edema of the face and ears and

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109 Naterman, H. L., and Robins, S. A. Cutaneous Test with Diodrast to Predict Allergic Systemic Reaction from Diodrast Given Intravenously, *J. A. M. A.* **119** 491 (June 6) 1942.

110 Sams, W. M., and Capland, L. Topical Treatment with Sulfathiazole, *Arch. Dermat. & Syph.* **44** 226 (Aug.) 1941.

## Book Reviews

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**El corazon y la circulacion en los hipertiroideos** By Hector Gotta, M.D.  
Pp 103, with 13 plates Buenos Aires Sebastian Amoriotu e Hijos, 1938

The author has prepared this book as a contribution to the study of the unsolved problems of hyperthyroidism. Its nine chapters begin with a study of the precordial area of patients who have hyperthyroidism, a study which in 1938 was published as a paper in the *ARCHIVES OF INTERNAL MEDICINE* (Gotta, H. Size and Shape of the Heart in Hyperthyroidism, *ARCH INT MED* **41** 860 [June] 1938). In the second chapter the shape of the heart of patients who have exophthalmic goiter is considered. The author finds that 33 per cent of patients with this disorder have a prominent left middle arc as an outstanding abnormal feature in the general configuration of the heart. This percentage decreases as age progresses, and the abnormality never has been noted to appear during the course of the disease or to disappear after complete recovery of the patient. Therefore, it must be considered to be a constitutional element, the author thinks, probably characteristic of persons in whom there is a tendency for the thyroid to become hyperfunctioning.

Electrocardiographic changes are discussed on the basis of study of 203 patients on whom 305 tracings were made. Full consideration of the subject led the author to the conclusion that there are not constant or specific variations in the tracings of patients who have exophthalmic goiter. The particular instance of the negative T wave in leads II and III, as encountered previously by Willis and Boothby in 3 patients, does not necessarily constitute a contraindication to thyroidectomy or an unfavorable prognosis.

Particular attention is given to auricular fibrillation associated with hyperthyroidism. The author feels that hyperthyroidism itself is an important factor in the production of such fibrillation, but because its frequency increases with the age of the patient, the author thinks that arteriosclerosis and hypertension also should be considered. As a general rule, he said, patients who have exophthalmic goiter and auricular fibrillation should be examined for associated cardiovascular disease, which usually is responsible for the enlargement of the precordial area that is encountered in a good number of cases. Subtotal thyroidectomy actually is the best treatment of auricular fibrillation in exophthalmic goiter, iodine and digitalis are the most helpful drugs to administer during the preoperative and postoperative periods, and quinidine has exceptional value in cases of persistent fibrillation after surgical removal of an adequate amount of glandular tissue.

In regard to blood pressure the author finds that an increased differential tendon occurs as a result of elevation of the systolic pressure and decrease of the diastolic pressure, the latter being more constant and more noticeable. Usually, he said, after cure of the hyperthyroidism, blood pressure returns to the values which obtained previous to the onset of the disease.

In discussing anatomic and physiologic aspects of the circulation in the presence of exophthalmic goiter the author places himself with those investigators who believe that hyperfunctioning of the thyroid gland does not produce specific or organic lesions of the myocardium. He thinks there are good reasons to consider the cardiac disturbances encountered in cases of this condition as purely functional disturbances.

Angina pectoris and cardiac failure frequently are associated with hyperthyroidism, and Gotta believes that in these conditions hyperfunction of the thyroid gland is an important precipitating factor. He remarked that a weak heart is not a contraindication to the surgical treatment of exophthalmic goiter, on the contrary, he declares it is an adequate indication for thyroidectomy.



sensitize him in the active and literal sense and so to demonstrate that the severe reactions following the reapplication depend on a change in the recipient rather than on any toxic property of the drug itself.

#### COMMENT

Once again I have tried to select and comment on those papers published during the last year which seemed to throw some light on the mechanism of allergy. The subject of allergy has been approached from many angles, and at first the various observations seem to be rather isolated. If, however, one turns the pages rapidly to skip many details and to consider the problem as a whole, there is one point which is common to them all.

The nature of the allergic response varies widely among different patients, evidently because different tissues are sensitized to different degrees. Landsteiner showed this in the sensitization of his animals to certain chemicals, Cripe's observations on twins demonstrated it, the Arthus phenomenon is obviously a local process. Pollens affect the noses of certain persons and the bronchi of others, and in the case of drugs the wide variation among the manifestations of drug allergy are always impressive. In other words, is it not clear that the symptoms of allergy depend on tissue reactions—in one tissue in 1 patient, in another tissue in another patient? Cutaneous tests are losing some of their glamour, because it appears that tissue sensitiveness may be quite localized, and the tissues involved may or may not include the skin. Such a concept is supported by the marked discrepancies which are observed so commonly. In hay fever, for example, one finds extensive cutaneous reactions in patients who have no symptoms to go with them. And then, on the other hand, as Colmes shows, there are patients who are clinically sensitive but in whom the results of cutaneous tests remain quite negative. In the case of diodrast Naterman finds that in certain patients whose cutaneous reactions to the drug are positive systemic reactions develop when it is injected. But, on the other hand, discrepancies occur in both directions, in some cases the cutaneous reaction was positive, but the treatment was given without reaction, while in a few other cases in which cutaneous tests yielded negative results, the treatment itself caused trouble. It looks, therefore, as though tissues and their reactions constituted the real problem in allergy. Studies of antibodies in the blood are always interesting, but their role is secondary.

The statement "If it was easy, it wouldn't be any fun" applies particularly to the study of allergy.

and Childhood, by Benjamin W Carey, Electroencephalography, by Major Normal Q Brill, The Role of Vitamin K in Hemorrhage in the Newborn Period, by H G Poncher, Persistent Ductus Arteriosus and Its Surgical Treatment, by Robert E Gross, The Premature Infant, by Abraham Tow, Tuberculosis, by Waldo E Nelson, Endocrinology, by Murray B Gordon, and Short Abstracts of Some Other Advances in Pediatrics, by Adolph G De Sanctis and George E Pittinos

The volume will undoubtedly be of greatest value to those persons who find it impossible to cover the current pediatric literature as it appears. The reviewer feels that in general the various articles could be presented in a much more condensed form, particularly since the original work has been published so recently and is so readily available.

The section on Toxoplasmosis, by Dr Albert B Sabin, rightly stands first in the volume as the most lucid and interesting contribution. Some subjects, such as cystic fibrosis of the pancreas, influenzal meningitis and the prophylactic use of sulfanilamide in rheumatic fever, seem to deserve more detailed coverage than is accorded them in the short abstracts in the final section.

"Advances in Pediatrics" should prove to be of inestimable value to the busy practitioner.

**Blood Substitutes and Blood Transfusion** By Stuart Mudd, M A, M D, professor of bacteriology, University of Pennsylvania School of Medicine, Philadelphia, and William Thalhimer, M D, director, Human Serum Division Public Health Research Institute of the City of New York, Inc. First edition. Hammermill straw. Price \$5. Pp 407. Springfield, Ill. Charles C Thomas, 1942.

This symposium-monograph is the work of many authors. Many of the papers were presented at the annual meeting of the American Human Serum Association held in June 1941, at Cleveland. Any advance work done on the particular subjects were included when the proofs were read this spring. The book is filled with information, interesting and valuable not only to the specialist, but also to the individual who is seeking an answer to many of the present day questions relating to whole citrated blood, blood plasma, blood serum and other blood substitutes. The book is ably summarized in the last chapter, "successful management of shock requires early recognition and effective measures for breaking the vicious circle. These will be directed toward removing the cause, toward increasing the blood volume and toward relieving anoxia." The four general methods of preserving plasma and serum are discussed. Points for and against each method are given. The merits of hemoglobin, serum albumin and casein digest as blood substitutes are discussed. The storage, transportation and administration of whole blood is ably presented. The Rh factor is discussed in a readily understandable manner. The specific A and B factors are shown to neutralize the anti-A and anti-B isoagglutinins found in group O blood. Reasons for and against the use of group O blood as from a universal donor are presented. On the whole, the book is interesting, informative and of value to general practitioner and specialist alike.

**Blutdruckmessung und Kreislauf in den Arterien des Menschen** By Heinrich von Recklinghausen. Pp 532, with 197 figures. Leipzig Theodor Steinkopff, 1940.

This amazing book is an exhaustive treatise on the theoretic and laboratory aspects of the human pulse and blood pressure. It would be difficult to discover any omissions of mathematical, physical or historical material, the book is evidently the result of a lifetime of patient collecting of material relating to hemodynamics. Every imaginable type of sphygmographic and sphygmomanometric device is illustrated and discussed. The historical notes are interesting and bear

A complete bibliography and a brief index constitute the final pages of this interesting monograph. It is well printed and thoroughly readable, and undoubtedly it will prove of considerable value to persons especially interested in cardiovascular and endocrine diseases.

**Internal Medicine in Old Age** By Albert Muller-Deham, M D, and S. Milton Rabson, M D. Price, \$5. Pp 396. Baltimore: Williams & Wilkins Co, 1942.

It hardly seems necessary to comment on a fact now well recognized, that gerontology is becoming an ever increasingly important division of medicine. The science of the changes, both physiologic and pathologic, that take place in the body of an aging person will naturally demand greater attention from members of the medical profession as human longevity becomes more and more extended. To meet the needs of practitioners there will be appearing from time to time books dealing with geriatrics. It is not entirely improbable that ultimately there may be as many textbooks, reference books and encyclopedias on the subject of old age as there are on pediatrics.

According to the preface, the authors of "Internal Medicine in Old Age" have for many years been interested in old patients. The senior author spent some fifteen years in Vienna and observed no less than 2,000 necropsies on elderly persons, as well as seeing these persons while alive. The junior author has likewise studied the pathology of senility for many years. The authors seem well qualified to prepare a book on this subject.

The first seven chapters have to do with general physiologic, hygienic and statistical facts of longevity. Then follows a series of chapters on the changes induced by aging in the respiratory system, the cardiovascular system, the urogenital system and the digestive system, with one chapter on blood dyscrasias, another on endocrine disorders, two on metabolism, three on the musculoskeletal system and one on infectious diseases. The greatest amount of space is devoted to the digestive system, a few more pages than those dealing with the cardiovascular system. There seems to be a disproportionate amount of space given to the digestive system in contrast to that given to the heart and blood vessels. It may be true, however, that old persons suffer from diseases of the digestive system and die of diseases of the cardiovascular apparatus. A disproportionately small amount of space is given to endocrine disorders, which are, after all, common in aged persons. The glands of internal secretion, which make up one division of the human system, practically always show the effects of old age to a greater or lesser degree, more often the former.

The book is thought provoking, well organized and well documented. In spite of the feeling of many physicians that not much can be done medically for old persons, the authors have given a considerable amount of space to the treatment of the various diseases they describe. The material on treatment is sufficiently specific to satisfy a practitioner who wants to know what to do for an old person who has intermittent claudication, diarrhea, paroxysmal dyspnea, nephritis, hypertension and so on. It might be added that the authors have not only written fully on what should be done but have wisely given considerable thought and space to what should not be done for elderly patients.

**Advances in Pediatrics** Edited by Adolph G. De Sanctis, M D. Associate Editors: L. Emmett Holt, M D, A. Graeme Mitchell, M D, Robert A. Strong, M D, and Frederick F. Tisdall, M D. Price, \$4.50. Pp 306. New York: Interscience Publishers, Inc., 1942.

The editors have compiled a collection of the most significant contributions to pediatric literature which have appeared during the past two years. Continuance of this volume as an annual review is proposed.

The book includes ten sections by various authors as follows: Toxoplasmosis. A Recently Recognized Disease of Human Beings, by Albert B. Sabin. Review of Virus Diseases, by Horace L. Hodes. Chemotherapy in Diseases of Infancy

## VENTRICULAR TACHYCARDIA

### AN ANALYSIS OF THIRTY-SIX CASES

CONGER WILLIAMS, M D

AND

LAURENCE B ELLIS, M D

BOSTON

Paroxysmal ventricular tachycardia is a rare condition. Numerous articles have, however, been published on the subject, although detailed case reports from a single hospital have not exceeded 6. In two articles Strauss<sup>1</sup> and Lundy and McLellan<sup>2</sup> reported a few cases and analyzed the literature. We here present and discuss 36 cases, to the best of our knowledge the largest series from one hospital.

The files of the Heart Station at the Boston City Hospital contain approximately 64,000 electrocardiograms taken over a period of twenty years. Seventy cases are listed in the cross index files under the diagnosis of ventricular tachycardia. Of this number we discarded 34 because the diagnosis was not certain. This makes the incidence of ventricular tachycardia 1 in every 1,800 tracings, confirming the general impression that the condition is rare. The patients were cared for by the various services of the hospital, and in only a few instances were they personally examined by us.

#### CRITERIA FOR THE ELECTROCARDIOGRAPHIC DIAGNOSIS OF VENTRICULAR TACHYCARDIA

Although sometimes ventricular tachycardia can be suspected by direct clinical observation, the diagnosis can be made with assurance only by means of the electrocardiogram. In some cases even then the diagnosis, though likely to be correct, is not beyond all doubt. The essential

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Read at the meeting of the New England Heart Association, Boston, March 24, 1941.

From the Thorndike Memorial Laboratory, the Second and Fourth (Harvard) Medical Services of the Boston City Hospital and the Department of Medicine, Harvard Medical School.

1 Strauss, M. B. Paroxysmal Ventricular Tachycardia, *Am J M Sc* **179** 337, 1930.

2 Lundy, C. L., and McLellan, L. L. Paroxysmal Ventricular Tachycardia. An Etiological Study with Special Reference to the Type, *Ann Int Med* **7** 812 1934.

witness not only to the cooperation of investigators of many different countries in advancing hemodynamics but to the broadness of the author's perspective

The book does not concern itself with questions of pathogenesis, diagnosis or biometry such as might arise, for instance, in life insurance work, consequently, its use to a practicing physician would be limited to occasional reference, for instance, on the construction and use of instruments like Pachon's oscilometer in cases of peripheral vascular disease. But for any one planning laboratory research in hemodynamics or wishing to devise new sphygmographic apparatus, many portions of this book would be of fundamental importance

**Changes in the Knee Joint at Various Ages** By Granville A. Bennett, Hans Waite and Walter Bauer. Price, \$2.50. Pp. 97, with 31 plates. New York: The Commonwealth Fund, 1942.

This handsome volume contains the results of part of a large research project on arthritis sponsored by the Commonwealth Fund, the Massachusetts Department of Public Health and the Robert W. Lovett Memorial Foundation. The original work deals with changes in the knee joint at various ages, but the volume really is a comprehensive treatise on "degenerative" arthritis. The interesting point is brought out that after the second decade degenerative changes in the knee joint become common. There are a full bibliography, beautiful plates and an adequate index.

**Cabot and Adams—Physical Diagnosis** By F. Dennette Adams. Price, \$5. Pp. 888, with 398 illustrations. Baltimore: The Williams & Wilkins Co., 1942.

In this thirteenth edition, under the editorship of Dr. Adams, Cabot's physical diagnosis carries on in able fashion. It is an interesting comment on modern specializations that the editor has called on consultants in various fields, so that what was originally a decidedly one man book now becomes to some extent a summation of the views of a group. Certainly in this process nothing of readability and usefulness has been lost.

**The Biological Action of the Vitamins** Edited by E. A. Evans, Jr. Price, \$3. Pp. 227. Chicago: University of Chicago Press, 1942.

This volume is a collection of fourteen papers on various subjects connected with nutrition and vitamins presented at a symposium held during the anniversary celebration of the University of Chicago. That the authors of the various contributions include such men as Elvehjem, Jolliffe, Gyorgy, Sebrell and Lepkowsky testifies to the quality of the papers.

**Introduction to Parasitology** By A. S. Pearse. Price \$3.75. Pp. 357 with 448 illustrations. Springfield, Ill.: Charles C. Thomas, Publisher, 1942.

This book, written from the biologic standpoint, seems to the reviewer to fill a real need of the practicing physician. Here in simple terms is a systematic discussion of parasites not only of man but of animals. The human parasitology is fitted into a sound general background. The numerous illustrations are an outstanding feature.

the left arm electrode in the third interspace at the right sternal border and exposing the film with the lead switch first in "Lead I" position and then in "Lead III" position. Thus, first the right arm and then the left leg is used as the indifferent electrode. In many cases, P waves are well shown in one of these special leads but not in the other.

Further evidence of the true nature of ventricular tachycardia may be found in control records taken before or after an attack, in the registration of the beginning or cessation of the paroxysm or in the demonstration of extrasystoles having the same appearance as the ventricular complexes seen in the attack.

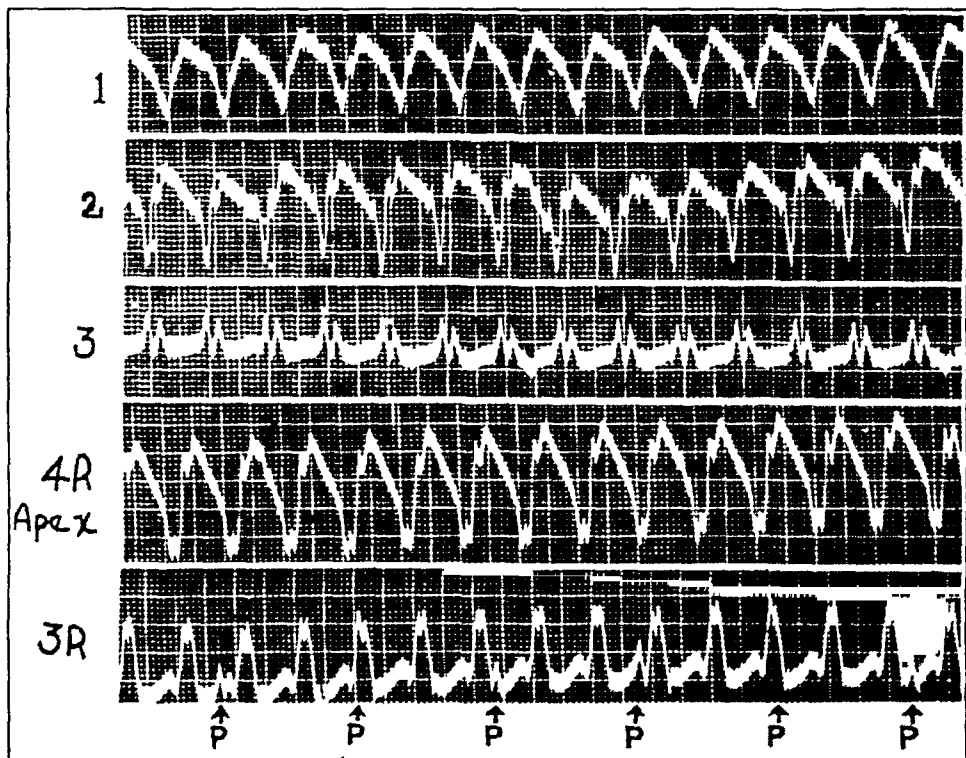


Fig 1—Paroxysmal ventricular tachycardia. The special auricular lead (marked 3R) shows P waves which do not appear in the standard leads. The auricular rate is 63, the ventricular rate, 150.

It is difficult to lay down absolute rules for diagnosis. The demonstration of an independent auricular rhythm is certainly sufficient. If this cannot be shown, one should have control records. In rare instances one can diagnose the condition with reasonable certainty from the bizarre nature of the ventricular complexes alone, but except in such rare instances other evidence is needed.

A more detailed discussion of the criteria for the diagnosis of ventricular tachycardia will be found in other articles.<sup>8</sup>

<sup>8</sup> Lundy and McLellan;<sup>2</sup> Robinson, G. C. and Herrmann, G. R. Paroxysmal Tachycardia of Ventricular Origin, and Its Relation to Coronary Occlusion, *Heart* 8:59, 1921. Wolferth, C. C., and McMillan, T. M. Paroxysmal Ventricular Tachycardia. Report of One Case with Normal Mechanism and Three with Auricular Fibrillation. *Arch. Int. Med.* 31:184 (Feb.) 1923.

point is to demonstrate an ectopic ventricular origin of the ventricular pacemaker, which always causes a prolonged QRS interval. Such ventricular complexes may, however, be produced in auricular and nodal tachycardia and even auricular flutter,<sup>3</sup> if there is a temporary aberrance of ventricular conduction, and can simulate ventricular tachycardia very closely, especially when the P waves are obscure. Any supraventricular tachycardia in the presence of permanent bundle branch block may produce the same picture.

In ventricular tachycardia the auricles may be stimulated by retrograde conduction to beat after each ventricular contraction or after every second beat. In the early work on the experimental production of ventricular tachycardia in dogs, Lewis<sup>4</sup> showed that such retrograde conduction can take place, and instances of its occurrence in man have been reported.<sup>5</sup> It is probable, however, that the usual mechanism is for the auricles to maintain an independent rhythm, usually slower than the ventricular rate. This was demonstrated in man by Palfrey,<sup>6</sup> who in 1913 showed by polygraphic tracings such an independence of the auricular and ventricular rhythms.

A diagnostic point of primary importance is therefore the demonstration of an independent auricular rhythm, usually at a slower rate. It may, however, be impossible to discern this, because the P waves are obscured by the QRS complexes or T waves, because of retrograde auricular conduction or because of the existence of auricular fibrillation.

The taking of a special auricular precordial lead is often helpful in demonstrating P waves when the other leads fail to bring them out. Although Lewis and others have used similar leads in the study of auricular rhythm, no reference to their use in ventricular tachycardia has appeared in the literature on that subject to our knowledge. Procedure for the taking of the special auricular lead was worked out in this department by Dr. J. M. Faulkner<sup>7</sup> and is followed routinely in the diagnosis of obscure disorders of rhythm. It has repeatedly cleared up an otherwise doubtful diagnosis (fig. 1). The lead is taken by placing

3 Maivim, H. M., and White, P. D. Observations on Paroxysms of Tachycardia, *Arch. Int. Med.* **29**: 403 (April) 1922.

4 Lewis, T. Experimental Production of Paroxysmal Tachycardia and the Effects of Ligation of the Coronary Arteries, *Heart* **1**: 98, 1909, Mechanism of the Heart Beat with Especial Reference to Its Clinical Pathology, London, Shaw & Sons, 1911, pp. 24, 168, 258 and 276.

5 Hart, T. S. Paroxysmal Tachycardia. The Paroxysms Arise from Impulses of Ventricular Origin, the Auricle Responds to the Ventricle, Evidence of Two Points of Ventricular Irritability, *Heart* **4**: 129, 1912. Scott, R. W. Observations on a Case of Ventricular Tachycardia with Retrograde Conduction *ibid.* **9**: 297, 1922.

6 Palfrey, F. W. Paroxysmal Tachycardia Confined to the Ventricles or to the Auricles, with Illustrative Cases, *M. & S. Rep. Boston City Hosp.* **16**: 182, 1913.

7 Faulkner, J. M. Unpublished data from the Heart Station, Boston City Hospital.

demonstrated by the use of that technic in some of the earlier records. Control records were available for comparison, however, in all but 1 of these 7 cases.

In no case was retrograde conduction to the auricle demonstrated. The proof of such conduction depends on the simultaneous recording of pulse tracings. This was not done in any of our cases.

Twelve cases (33 per cent) were classified as intermittent ventricular tachycardia. Normal strips in the same record for comparison with the tachycardia made the diagnosis easier, and an independent auricular rhythm could be more readily identified. Most of the records showed ventricular extrasystoles, and all showed abrupt onset or cessation.

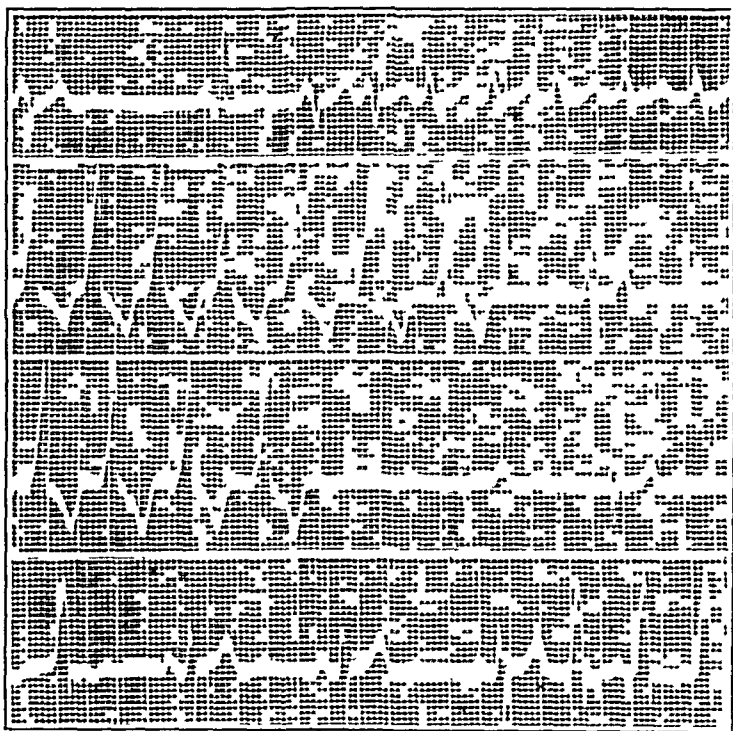


Fig. 3—Ventricular tachycardia of the intermittent type. A run of ventricular tachycardia can be seen in each lead. The auricular rhythm is undisturbed and is easily identified through the periods of tachycardia.

of the tachycardia. Although technically ventricular tachycardia may be considered to be present when two or more ventricular extrasystoles occur in rapid succession, we have included cases in the series only if the run of tachycardia persisted for at least ten beats, in the majority of cases it was longer.

The incidence of auricular fibrillation as shown by control records (39 per cent) compares with that observed by Strauss<sup>1</sup> in his analysis of a large number of cases taken from the literature on ventricular tachycardia. It is interesting to observe that 2 patients with the intermittent type of tachycardia who showed auricular fibrillation before and during



## RESULTS

*Persistent Versus Intermittent Tachycardia*—For the purpose of analysis, the cases of ventricular tachycardia in our series were divided into two types. In the majority of tracings taken during an attack, all beats appeared to be of ventricular origin and each record presented a fairly uniform appearance (fig 2). This group was arbitrarily designated "persistent" ventricular tachycardia. In one third of the cases, runs of ventricular tachycardia were separated by periods of normal rhythm, the latter often showing ventricular extrasystoles. Cases showing this type of tracing were called "intermittent" ventricular tachycardia (fig 3). The subdivision of ventricular tachycardia on this basis is of course purely arbitrary, and it is quite possible that 1 case might show

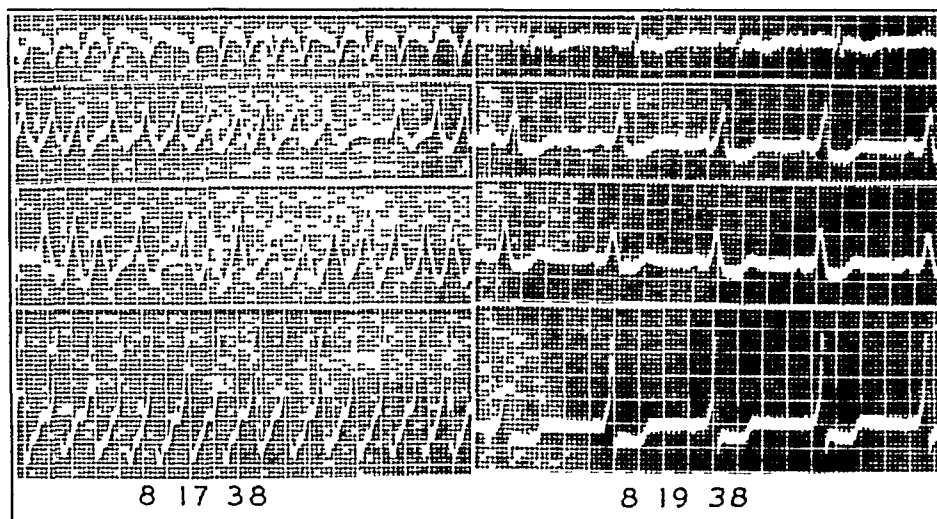


Fig 2—Ventricular tachycardia of the persistent type, showing slight irregularity of the ventricular rhythm. The control record, taken two days later, shows intraventricular block (QRS 0.12 second) and slightly prolonged Q-T interval (quinidine effect [?]). The T waves, which suggest digitalis effect, became normal in subsequent records.

each type of tracing if records were taken at appropriate times. However, in all cases in which several records were taken during the attack, the rhythm was consistently of one type or the other. This classification aids the study of the duration and prognosis of attacks and the results of therapy.

Twenty-four cases (66 per cent) were classified as persistent ventricular tachycardia. It was possible to demonstrate an independent auricular rhythm in 11 patients; of the remaining 13, 6 showed auricular fibrillation in records taken before or after the attack, and 7 showed no P waves during the attacks. The special auricular lead was not used in this department until 1937, and it is possible that P waves might have been

The exception was our only patient with the alternating bidirectional type which is usually attributed to the toxicity of digitalis<sup>10</sup>

*Disturbances in Conduction*—In our series the incidence of disturbances in conduction was rather low (table 1) All disorders so listed were shown in control records before the onset of the paroxysm except intraventricular block, in cases of which the controls were taken after

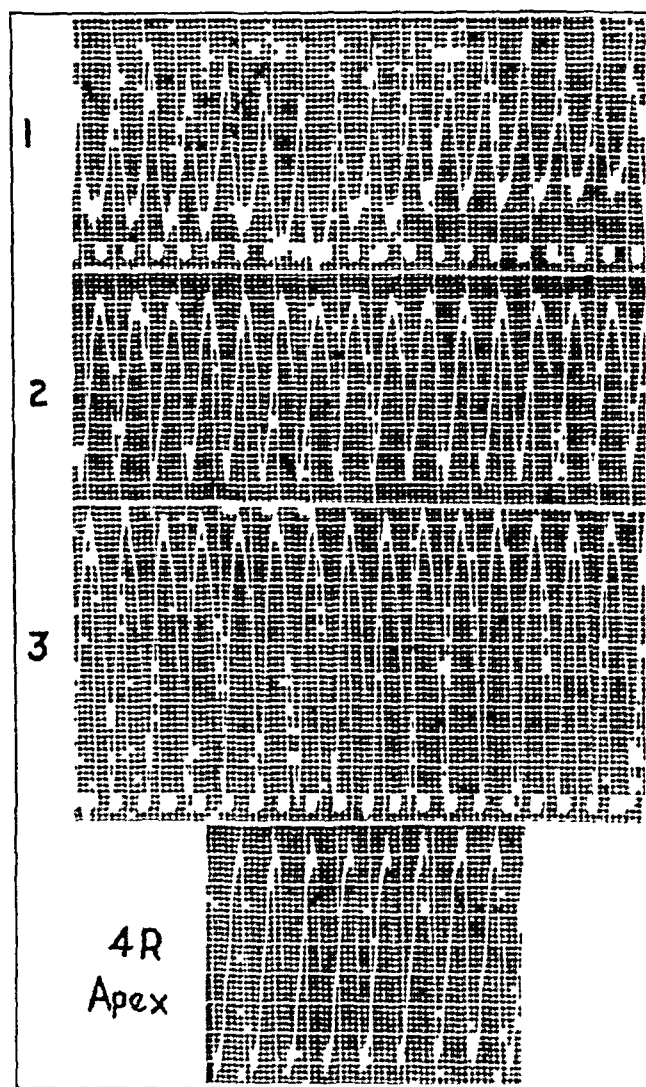


Fig 4 (July 9, 1940)—Persistent ventricular tachycardia (rate 250) showing striking regularity of oscillation

10 (a) Palmer, R S, and White, P D Paroxysmal Ventricular Tachycardia with Rhythmic Alternation in the Direction of the Ventricular Complexes in the Electrocardiogram, *ibid* 3 454, 1927 (b) Marvin, H M Paroxysmal Ventricular Tachycardia with Alternating Complexes Due to Digitalis Intoxication, *ibid* 4 21, 1928 (c) Scherf, D, and Kisch, F Ventricular Tachycardias with Variform Ventricular Complexes, *Bull New York M Coll, Flower & Fifth Ave Hosps* 2 73, 1939

the attack returned to normal sinus rhythm within five and fourteen days respectively after the end of the attack. One patient received quinidine, the other did not.

*Detailed Analysis of the Electrocardiograms* (table 1)—In the majority of cases records taken before or after the attack during the same hospital admission were available for comparison. In 27 cases more than one record was taken, five or more were taken in 10 cases and in 1 case thirteen were taken.

Ventricular rates ranged from 110 to 250. In 32 cases the ventricular rate was faster than 130, in 10 it was faster than 170, and in 5 it was faster than 200. The two patients with the most rapid rates, 250 and 220 per minute, which were present on admission and persisted eight hours and two days after admission respectively, recovered and were discharged improved.

TABLE 1—*Associated Electrocardiographic Abnormalities*

	Number of Cases	Percentage of Total
Auricular fibrillation	14	39
Shifting auricular pacemaker	2	6
Disturbances in conduction (in control records)		
Complete heart block	1	4
Incomplete auriculoventricular block	1	4
Intraventricular block (QRS = 0.11–0.12 sec.)	7	19
A-V dissociation	1	4

The duration of QRS ranged from 0.12 second to 0.20 second. In 20 cases it was more than 0.14 second.

Records were examined to determine the regularity of the ventricular rhythm, because slight irregularity to auscultation is one of the points on which the diagnosis of ventricular tachycardia without the aid of the electrocardiogram is based.<sup>9</sup> The brief period during which a record is taken does not of course necessarily indicate what may occur over a longer period. In 1 case in which a continuous tracing was taken for five minutes, the record was regular except for three brief periods in each of which one ventricular beat was apparently "dropped."

In the 24 cases of the persistent type, only 4 records showed obvious irregularities of the ventricular rhythm (fig. 2). All but 1 showed a striking uniformity in the appearance of the ventricular beats, indicating uniformity in the point of origin. In 1 case there was a temporary irregularity in the appearance of the QRS complexes.

Of the 12 patients with the intermittent type, all but 1 showed uniform, regular QRS complexes during runs of ventricular tachycardia.

<sup>9</sup> Levine, S. A. The Clinical Recognition of Paroxysmal Ventricular Tachycardia, *Am. Heart J.* 3:177, 1927.

the disorders just mentioned or angina pectoris or myocardial infarction in the absence of any other possible cause for the disorder. The usual criteria were used in classifying the other cases as they are listed<sup>11</sup>

As might be expected from the age distribution, so-called degenerative heart disease was present in 28, or 78 per cent, of the patients. Only 4 patients had unmistakable valvular involvement. Two of these had rheumatic mitral disease, 1 calcareous aortic stenosis and 1 syphilitic aortitis with aortic insufficiency and aneurysm of the ascending aorta. Many other patients had systolic murmurs without other evidence of valvular disease.

A number of cases of paroxysmal ventricular tachycardia occurring in persons without heart disease have been reported in the literature. It is probable that our series does not give a true indication of the relative occurrence of ventricular tachycardia in persons with and without heart disease. Most of our records were from hospitalized patients whose attacks had persisted long enough to permit the taking of an electrocardiogram. Persons without organic heart disease are likely to have attacks of short duration and are less likely to be studied in an attack.

*Congestive Heart Failure*—The incidence of congestive failure in this series was high. The figure given in table 2 (86 per cent) refers to the percentage of patients with failure at the time of admission. In 8 of these ventricular tachycardia was present on admission, so it is not known whether the failure or the tachycardia came first. In 23 cases failure preceded the attack of ventricular tachycardia. In no patient could it be definitely shown that the attack precipitated congestive failure, although the failure was aggravated during the tachycardia in at least 2 cases. These facts are not surprising in view of the high percentage of underlying heart disease and the importance of toxicity due to digitalis as a precipitating factor in this type of tachycardia. Five of the 9 cases in this group were of the persistent type of tachycardia.

*Precipitating Factors* (table 3)—Toxicity due to digitalis was associated with the attack more often than any other single factor. We included in this group only those patients that had received at least twice the dose theoretically necessary for digitalization. In 3 cases definite symptoms of toxicity were recorded (nausea, vomiting, yellow vision). Four of the 8 cases in this group were of the persistent type of tachycardia.

In the group labeled "digitalis (?)" dosage of the drug was somewhat in excess of the theoretic requirement, and no other cause for the attack was apparent.

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11 Nomenclature and Criteria for Diagnosis of Diseases of the Heart, ed 4, New York, New York Heart Association, 1939

the paroxysm. No cases of bundle branch block were encountered in this series. However, the low incidence of observed disturbances in conduction is not necessarily significant, because the time between control records and those taken during the attack varied greatly. Some were taken weeks or longer before or after the attack.

*Relation to Age and Sex*—The preponderance of the older age groups is striking. Ninety-four per cent of the patients were over 40 years of age, and 52 per cent were over 60. Three fourths of the attacks occurred in men. These findings agree in general with those published in other series, but differ in that in our series there is no patient under the age of 30.

*Underlying Heart Disease* (table 2)—In only 1 case could it be definitely said that there was no underlying heart disease. The patient

TABLE 2—*Underlying Heart Disease*\*

No heart disease	1 case		
Definite evidence of underlying heart disease	35 cases		
Congestive failure	31 cases		
Distribution of Types of Heart Disease			
	Cases	Percentage	Autopsy
1 Arteriosclerotic	17	47	3
2 Hypertensive	4	13	
3 Hypertensive and arteriosclerotic	11	31	4
4 Rheumatic	1	3	
5 Rheumatic and hypertensive	1	3	
6 Syphilitic	1	3	1
	<hr/> 35	<hr/> 100	<hr/> 8

\* In groups 1 and 3 together, there were 6 definite instances of acute myocardial infarction (4 proved by autopsy). In 2 more instances this was a good possibility.

had a normal cardiac history, the results of physical examination were normal, and a teleoroentgenogram of the heart was also normal. She was the next to the youngest in the series (aged 37), and the precipitating cause of her attacks of ventricular tachycardia was unknown. The attacks of tachycardia were of the intermittent type and had apparently occurred for many years.

Another patient, the youngest, aged 34, was a woman with an enlarged heart, a loud apical first sound and systolic murmur and slight hypertension, but with no cardiac disability except palpitation and a sense of oppression in the chest during her attacks, which had occurred for at least two months and probably for much longer and were also of the intermittent type. She was considered to have rheumatic and hypertensive heart disease with involvement of the mitral valve. All of the other patients showed cardiac enlargement, disorders in rhythm or clear evidence of cardiac failure. The underlying heart disease was called arteriosclerotic in those patients of the proper age who showed any of

sisted at a rate varying from 137 to 167 she complained only of weakness and palpitation. After the attack had commenced she was given about 27 to 36 grains (1.75-2.33 Gm.) (exact quantity uncertain) of digitalis in three days and was then maintained on a daily dose of  $1\frac{1}{2}$  grains (0.09 Gm.) for four weeks thereafter. Quinidine was given in varying amounts, with a maximum of 40 grains (2.59 Gm.) daily for seven days from the twenty-third to the thirtieth day of the attack. After spontaneous cessation of the attack her condition was but little altered. Pneumonia then developed, and she died a week later. Permission for autopsy was refused.

In our series there was no demonstrable relationship between mortality and heart rate, width of QRS or the type of the complexes, whether they were of the left or the right ventricular type.

TABLE 3—*Probable Precipitating Factors Associated with Thirty-Seven Attacks in Thirty-Six Patients with Ventricular Tachycardia*

Precipitating Factors of Ventricular Tachycardia	Persistent Type			Intermittent Type			Total Attacks
	Died in Attack	Died Later in Hospital, Within 1 Month	Recovered	Died in Attack	Died Later in Hospital, Within 1 Month	Recovered	
Digitalis	1	3	0	0	2	2	8
Digitalis and quinidine	0	0	1	0	0	0	1
Digitalis (?)	2	1	1	1	1	3	9
Myocardial infarction	3	2*	0	0	1	0	6
Myocardial infarction (?)	0	0	3	0	0	0	3
Miscellaneous	1	1	3	0	0	2	5
Unknown	0	2	1	0	0	2	5
Total	7	9	9	1	4	7	37

\* One of these patients died of a fresh myocardial infarction two months after the attack stopped.

What does influence the prognosis is the nature and degree of underlying heart disease. This is brought out most clearly in an examination of the mortality figures in the cases in which the precipitating factors were digitalis and myocardial infarction respectively. All 6 of the patients with definite myocardial infarction died, 3 of them in the attack, although the 3 in whom cardiac infarction was doubtfully present recovered. Six of the 8 who had had marked overdosage with digitalis also succumbed, though only 1 died in the attack. Five of the 9 to whom a moderate overdosage of the drug had been given also died. All of these patients had severe heart disease. In contrast, the patient with no heart disease is alive and well except for her attacks, as is the patient with probable mitral stenosis, who has had intermittent attacks for two months or longer, and 3 of the 5 in whom attacks occurred in association with noncardiac acute episodes are also living, the other 2 having died of uremia and cerebral hemorrhage respectively.

One patient who had had excessive doses of digitalis had also received quimidine sulfate in large amounts (60 to 100 grains [3.88-6.48 Gm] daily for four days) before the onset of the attack. In his case either drug or both in combination may have been a factor in precipitating the attack.

Acute myocardial infarction was present at the time of the attack in 6 cases, in 4 infarction was proved by autopsy and in the other 2 it was clinically evident and supported by classic changes in the electrocardiogram. Although the statement has been made that when ventricular tachycardia occurs in association with myocardial infarction it usually follows the administration of digitalis, only 2 of our 6 patients with myocardial infarction had received digitalis before the onset of ventricular tachycardia, and these had not had an excessive dose.

The group labeled "myocardial infarction (?)" presented suggestive but not conclusive evidence in the absence of other known cause.

Only 1 patient in our series had two distinct proved prolonged attacks of ventricular tachycardia. These were separated by a time interval of eight months. The patient died during the second attack, and autopsy revealed recent and healed myocardial infarctions. However, only the second attack was considered to have definite relationship to an acute infarction, because the time relationship of the first was somewhat uncertain. In the majority of cases the tachycardia followed infarction within a few days.

The "miscellaneous" group included 5 patients in whom an acute episode bore a close time relationship to the onset of the attack. The associated acute episodes were an injury received in an automobile accident followed by a fight, a cerebral vascular accident, uremia, cholelithiasis and an embolus to the femoral artery. No attempt will be made to evaluate this association.

*Outcome of Attacks and Mortality* (table 3) —There were 21 deaths during or after the attack of ventricular tachycardia (67 per cent) but only 8 patients died in the attack itself.

Although the duration of attacks during hospitalization (5 attacks were present on admission) of these 8 patients varied from four hours to five days, it was impossible to prove that the length of the attacks affected the mortality. The patients who recovered from the attacks and were discharged improved had in many instances attacks of equal or longer duration, although, with an exception to be noted, no attack lasted longer than nine days after admission.

One patient deserves special mention, since her attack lasted for six weeks. She was a woman aged 74 with severe degenerative heart disease. The attack developed without known precipitating cause seven weeks after an exploratory laparotomy, and during the six weeks it per-

the thirteenth day of the attack respectively. In the first the ventricular rate increased 9 beats per minute, and in the second it decreased 12 beats in the time intervals mentioned. After quinidine was given, the rhythm in the first patient returned to normal, and in the second the ventricular rate slowed 22 beats per minute in four days' time.

#### COMMENT

It is generally agreed that toxicity due to digitalis and myocardial infarction are precipitating factors of ventricular tachycardia and that myocardial disease is present in most cases. Formerly hyperirritability of the myocardium induced by any of these factors was emphasized as the provoking cause. This was thought to create a center of excitation in one or several places in the ventricle. Circus movement of the exciting impulse in the ventricle has been suggested as the cause of ventricular tachycardia of the alternating bidirectional type.<sup>12</sup> Davis and Sprague<sup>13</sup> in reporting a case from this hospital<sup>14</sup> suggested that ventricular fibrillation, and possibly ventricular tachycardia, might be the result of a circus movement in the ventricles. Occasional records seem to support this thesis. One of our tracings shows a perfectly regular wavelike oscillation of the ventricular impulse at a rate of 250 per minute (fig. 4), but the rapid rate may account for the wavelike oscillation. It is also of interest that in this case intraventricular block was shown in subsequent control records. Davis and Sprague expressed the opinion that the conduction system of the ventricle normally tends to prevent circus movement because of its ability to conduct impulses rapidly to all parts, and that factors which depress the His-Purkinje system remove this inhibiting influence. Davis<sup>15</sup> discussed the relation of digitalis toxicity, bundle tissue disease (bundle branch block) and myocardial infarction to ventricular tachycardia. He expressed the opinion that the depressing effect of digitalis on auriculoventricular conduction time preceding ventricular tachycardia,<sup>16</sup> as well as the possible temporary disturbance in the conduction system in myocardial infarction, might be related to the arrhythmia. Herrmann and Ashman<sup>17</sup> expressed somewhat similar ideas with

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12 Palmer and White<sup>10a</sup> Marvin<sup>10b</sup>

13 Davis, D., and Sprague, H. B. Ventricular Fibrillation. Its Relation to Heart Block, *Am Heart J* **4** 559, 1928

14 This case is not included in our series

15 Davis, D. Ventricular Tachycardia. An Interpretation of the Nature of Its Mechanism, *Am Heart J* **7** 725, 1932

16 Luten, D. Clinical Studies of Digitalis, *Arch Int Med* **35** 74 (Jan.) 1925

17 Herrmann, G. R., and Ashman, R. Partial Bundle Branch Block. A Theoretical Consideration of Transient Normal Intraventricular Conduction in the Presence of Apparently Complete Bundle Branch Block, *Am Heart J* **6** 375 1931



In general the intermittent type of tachycardia carried a somewhat less serious prognosis than the persistent type, since 7 of the patients with the former type survived, in contrast to but 9 of 24 of those with the latter. Moreover, in instances in which overdosage with digitalis may have been a factor, 9 patients had the persistent type and 7 died, and 9 had the intermittent type and only 4 died.

*Quinidine Therapy*—The results of quinidine therapy are very difficult to evaluate because the patients were not uniformly treated or studied with especial care, because the dosage of quinidine was rather low and because of the possibility of spontaneous cessation of the attack. For these reasons it seemed unprofitable to analyze in detail the results of quinidine therapy in our series. Of the 24 patients with persistent tachycardia (25 attacks), 15 received quinidine but to only 12 of the latter (13 attacks) was it given in significant amounts (average of 15 grains [0.97 Gm.] to 70 grains [4.53 Gm.] daily, with a mean of 24 grains [1.55 Gm. of quinidine sulfate]). The duration of attacks after the initiation of quinidine therapy ranged from eight hours to four weeks and appeared to be fully as long as or longer than that of the untreated attacks. Seven of the 12 patients (13 attacks) receiving quinidine recovered, 3 died in the attack and 3 in the hospital subsequent to the attack. Two of the 11 patients receiving little or no quinidine recovered, 4 died in the attack and 5 after its cessation. Too many factors were involved to permit the drawing of any conclusions as to the efficacy of quinidine in this series.

Only 2 of the patients with the intermittent type of tachycardia were given quinidine in more than minimal doses. One died in the attack, the attack of the other stopped in twenty-four hours and recovery occurred.

One patient in whom ventricular tachycardia developed four days after a cerebral accident was given an unspecified amount of a 3 per cent solution of a quinine salt intravenously, and the attack ceased two hours after the injection was stopped. The patient died of the effects of the cerebral episode a day later.

It has been observed that quinidine often produces a slowing of the ventricular rate during the paroxysm of tachycardia. This phenomenon was studied by observation of the ventricular rate in the electrocardiogram. Of the 14 patients whose attacks were treated with quinidine, 4 had only one record taken during the paroxysm and 3 showed no slowing of the ventricular rate. In the other 7 definite slowing was observed, the minimum being 9 beats per minute, the maximum 112 beats and the mean 24. It would have been interesting to compare these findings with those of a similar group of untreated patients, but only one electrocardiogram was taken during the attack for each untreated patient. However, there were 2 patients who did not receive quinidine until the sixth and

instances In no case was there a history of typical anginal attacks between paroxysms of tachycardia White <sup>22</sup> commented on the rarity of angina of effort in patients who have pain during a paroxysm of tachycardia but stated "Finally, angina pectoris is induced in rare cases as a status anginosus by paroxysmal auricular fibrillation, paroxysmal auricular flutter, or tachycardia in patients who have already shown angina pectoris on effort"

It may be difficult or impossible to exclude myocardial infarction as a cause of pain during a paroxysm of ventricular tachycardia Two of the patients in our series who complained of severe substernal pain during the paroxysm of tachycardia showed no clinical or laboratory evidence of myocardial infarction before or after, and there was no history of angina, although both showed cardiac enlargement and were diagnosed as atherosclerotic heart disease One of the patients in our series gave a definite history of angina pectoris, but did not complain of pain during the attack Several patients were conscious of rapid cardiac action, which they described as palpitation or fluttering of the heart

As has already been stated, in none of our cases have we proof that the onset of the tachycardia precipitated congestive heart failure, although in 2 a previously existent failure was aggravated It is, however, well known that tachycardia of any type may produce congestive heart failure in a person with organic heart disease

*Clinical Diagnosis*—Any tachycardia, especially if it is paroxysmal, may be of ventricular origin, but it rarely is If the patient has degenerative heart disease, and particularly if there is a myocardial infarction or a large overdose of digitalis, the likelihood of its existence is increased As Levine <sup>9</sup> pointed out, one can on occasion make a presumptive diagnosis by direct examination if (1) the rhythm is rapid and essentially regular but slight irregularities can be detected, (2) the quality of the first heart sound varies in intensity in some of the cycles, or (3) attempts at "vagal" (carotid sinus) or ocular pressure prove ineffective in slowing the heart None of these criteria is, however, constantly present or helpful Many persons with ventricular tachycardia show no irregularity whatsoever Variation in the first heart sound is a useful sign but depends on a varying relationship between auricular and ventricular contraction and hence is most helpful in cases with an independent auricular rhythm It is not likely to occur when the auricles are fibrillating or if there is retrograde, ventriculoauricular conduction Finally although it is generally stated that ventricular tachycardia does not respond to vagal stimulation, often there is no such response in cases

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<sup>22</sup> White, P. D., and Camp, P. D. The Status Anginosus Induced by Paroxysmal Auricular Fibrillation and Paroxysmal Tachycardia, *Am Heart J* 7: 581, 1931

regard to bundle branch block Miller<sup>18</sup> has recently presented a good summary of the state of opinion on this question and has reported a case of ventricular tachycardia with myocardial infarction involving the interventricular septum. Transient bundle branch block was observed between paroxysms. Two cases with autopsies have been recently reported in which the arrhythmia followed a lesion of the septum due to syphilis.<sup>19</sup>

Thus the relationship of disturbances of conduction and ventricular tachycardia has been suggested, but the importance of such defects of conduction in relation to other factors has not been shown, nor has the question of coincidence been eliminated.

*Symptoms Associated with Ventricular Tachycardia*—Tachycardia per se may give rise to symptoms due to circulatory insufficiency. The site of these symptoms depends in the main on the relative degree of underlying arterial disease in various parts of the body. Cerebral manifestations (vertigo, fainting, temporary blindness, epileptiform seizures) have been reported by Barnes<sup>20</sup> and are presumably the result of cerebral anoxia. Only 1 of our patients is known to have had cerebral symptoms related to tachycardia. He lost consciousness at the onset of his attack.

The varying degrees of general circulatory collapse (shock) which occur with tachycardia are due primarily to the difficulty in maintaining an adequate cardiac output in the presence of the rapid rate and short diastolic pause. It has not proved practicable to analyze our cases with respect to the occurrence and degree of shock, although in several it was profound.

Patients may complain of pain or discomfort in the chest during an attack, although this is not a common symptom. Barnes and Willius<sup>21</sup> report 19 instances of precordial or substernal pain occurring in 380 cases of paroxysmal tachycardia of all types. The pain was described as aching or lancinating, and in some cases there was a sensation of constriction or oppression. Radiation to the arms occurred in a few

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18 Miller, H. Transitions Between Normal Intraventricular Conduction, Bundle Branch Block and Ventricular Tachycardia. Report of a Case, *Am Heart J* **19** 364, 1940.

19 Cossio, P., Vivoli, D., and Caul, H. Syphilis of the Interventricular Septum and Ventricular Tachycardia, *Am J M Sc* **194** 369, 1937. Coelho, E., and de Oliveira, A. Syphilis of the Intraventricular Septum and Ventricular Tachycardia. Syphilis of the Pulmonary Artery, *Arch d mal du cœur* **32** 17, 1939.

20 Barnes, A. R. Cerebral Manifestations of Paroxysmal Tachycardia, *Am J M Sc* **171** 489, 1926.

21 Barnes, A. R., and Willius, F. A. Cardiac Pain in Paroxysmal Tachycardia, *Am Heart J* **2** 490, 1926.

been taken on patients with ventricular tachycardia at the moment of death. However, these have shown that either ventricular fibrillation <sup>26</sup>, or ventricular standstill <sup>27</sup> may be the terminal event.

*Therapy*—As has been stated, simple measures such as pressure on the eyeball and pressure on the carotid sinus, which are often effective in auricular tachycardia, are rarely of benefit in the treatment of ventricular tachycardia. Digitalis is best omitted if it has been used before the attack. Moreover, because we believe that digitalis was a causal factor in some of our cases, we are doubtful of the wisdom of using it in the treatment of an attack even when no digitalis has been taken. Quinidine has been and still is widely used because of its depressant effect on ventricular conductivity. The use of quinidine dihydrochloride intramuscularly has recently been reported <sup>28</sup>. Potassium chloride and magnesium sulfate have been used, but a definite evaluation of their worth is not yet possible. Both of these drugs have been tried in this hospital, with equivocal results with the former and negative results with the latter drug.

It is not possible to formulate a rigid set of rules governing dosage of quinidine, and the choice between the oral and the intravenous route is still a matter of opinion. The usual oral dose of 3 grains (0.19 Gm.) of quinidine sulfate as a test for sensitivity is advisable in every case. If the drug is to be given by mouth, it is best to plan a regimen of repeated doses at intervals of two or three hours, in view of the fact that its duration of action is brief and the situation is urgent. It is then possible to adjust the dosage to the response of the patient. Thus if 6 grains (0.39 Gm.) is given every two hours the total amount given at the end of twelve hours will be 36 grains (2.33 Gm.). If the tachycardia still persists the dosage can be increased, provided that no signs of toxicity have been observed. Levine and Stevens <sup>29</sup> stressed the necessity for adequate dosage and cited the case of a patient with ventricular tachycardia following myocardial infarction which proved refractory to treatment until the daily dosage reached 112 grains (7.24 Gm.). Daily doses up to 90

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26 Thompson, I. Ventricular Fibrillation Causing Sudden Death of a Patient with Disease of the Left Coronary Artery, *J. A. M. A.* **116** 2583 (June 7) 1941.

27 Miller <sup>18</sup> Grieco, E. H., and Schwartz, S. Observations on the Mechanism of the Dying Heart in a Patient with Ventricular Tachycardia, *Am. Heart J.* **16** 595, 1938.

28 Riseman, J. E. F., and Linenthal, H. Paroxysmal Ventricular Tachycardia. Its Favorable Prognosis in the Absence of Acute Cardiac Damage and Its Treatment with Parenterally Administered Quinine Dihydrochloride, *Am. Heart J.* **22** 219, 1941.

29 Levine, S. A., and Stevens, W. B. The Therapeutic Value of Quinidine in Coronary Thrombosis Complicated by Ventricular Tachycardia, *Am. Heart J.* **3** 253, 1927.

either of auricular tachycardia or of flutter, so this is by no means a clearcut differential point. Moreover, it is not impossible that on occasion such vagal stimulation may be effective in ventricular tachycardia. Although vagal stimulation did not stop the attacks in any case in the present series, we have recently observed 2 patients in whom the paroxysms were stopped by pressure on the carotid sinus (in 1 patient on two occasions). The cases of these patients fulfil most of the electrocardiographic criteria for paroxysmal ventricular tachycardia, since in both the ventricular complexes differed markedly from the QRS complexes in control records. Since auricular fibrillation was present in each case, an independent auricular rhythm could not be demonstrated. Because unfortunately the moment of onset or cessation of the attack was not recorded electrocardiographically, and because paroxysmal auricular flutter or even some other type of ectopic rhythm with aberrant ventricular response could not be unequivocally excluded, these cases have not been included in this series.

*Prognosis*—It is difficult to estimate the importance of ventricular tachycardia in relation to mortality in most cases because of the severity of the underlying heart disease. Theoretically, rapid heart rate sustained for any length of time hastens myocardial exhaustion. This leads to increased ventricular irritability and raises the chances of ventricular fibrillation.

Various authors<sup>23</sup> have reported that the minute volume output of the heart during paroxysmal tachycardia is reduced by one tenth to two thirds of the normal output. One study of the blood gases during paroxysmal auricular tachycardia<sup>24</sup> showed a decrease in the degree of arterial oxygen saturation, a low oxygen saturation of venous blood and an increased coefficient of utilization.

Fall in blood pressure which sometimes accompanies paroxysmal tachycardia may also hinder the circulation. Tachycardia of any kind may precipitate or increase the severity of cardiac failure.<sup>25</sup> This was seen in at least 2 of our cases. The cerebral symptoms we described are probably related to decreased cardiac output and cerebral blood flow. It would seem at least possible, therefore, that in the presence of extensive heart disease prolonged tachycardia might be fatal. Few records have

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23 Barcroft, J., Bock, A. V., and Roughton, F. J. Observations on the Circulation and Respiration in a Case of Paroxysmal Tachycardia, *Heart* 97, 1921. Schone, G. The Magnitude of the Circulation in Paroxysmal Tachycardia, *Klin Wchnschr* 16 804, 1937.

24 Carter, E. P., and Stewart, H. J. Studies on the Blood Gases in a Case of Paroxysmal Tachycardia, *Arch Int Med* 31 390 (March) 1923.

25 Boyer, N. H., Leach, C. E., and White, P. D. Underlying Causes and Precipitating Factors of Congestive Heart Failure, in *Blood, Heart and Circulation Symposium*, Publication 13, American Association for the Advancement of Science, 1940.

available for intramuscular use, quinine dihydrochloride may be used in dosages up to  $7\frac{1}{2}$  grains (0.5 Gm.), repeated if necessary at hourly intervals.

Kerr<sup>32</sup> stated that he seldom used quinidine in any form in ventricular tachycardia. He expressed the opinion that it is especially contraindicated in the presence of myocardial infarction, since "the conduction mechanism may be damaged and quinidine may further depress its activity, leading to ventricular fibrillation." Davis and Spague<sup>13</sup> for the same reason suggested (in the treatment of any disorder) that quinidine be used with care in combination with digitalis in the presence of combined auriculoventricular and intraventricular block. It is probable that quinidine may itself occasionally precipitate ventricular tachycardia or fibrillation, theoretically, the chances of its doing so are increased when it is used in combination with digitalis or in the presence of disturbances of conduction. In 2 of the cases reported by Hepburn and Rykert,<sup>31</sup> ventricular tachycardia followed the treatment of auricular fibrillation by the oral administration of quinidine sulfate. This occurred in 1 of our cases, but the patient had received a large overdose of digitalis as well. Schwartz and Jezer<sup>33</sup> reported the precipitation of attacks of transitory ventricular fibrillation by both quinidine and quinine in 2 patients in whom the attacks also occurred spontaneously.

The theoretic objections on the ground that quinidine produces conduction disturbances and thus may prolong the attack or induce ventricular fibrillation are outweighed by the many reports attesting to its usefulness. Full appraisal of its value will necessarily be slow. Proved fatalities directly traceable to quinidine have been few, but that should not diminish care in the use of the drug. Repeated electrocardiograms are advisable, especially with intravenous injection, and if the latter method is used it is well to have frequent checks on the blood pressure.<sup>30</sup> It has proved impossible to draw definite conclusions from our series as to the value of quinidine therapy, and in general it is difficult to prove the usefulness of this drug by statistical evidence. In certain individual cases the value of quinidine or similar substances seems unquestioned. Even if the drug does not abolish the attack, a slowing of the ventricular rate often occurs and produces improvement in the circulation.

#### SUMMARY AND CONCLUSIONS

1. An analysis is reported of 36 cases of paroxysmal ventricular tachycardia. In 24 the electrocardiograms showed the attack to be uninterrupted, and in 12 the attacks occurred in short runs of tachycardia.

32 Kerr, W. J. Use of Quinidine in Cardiac Irregularities, in Stroud, W. D. Diagnosis and Treatment of Cardiovascular Disease, Philadelphia, F. A. Davis Company, 1940.

33 Schwartz, S. P., and Jezer, A. The Action of Quinine and Quinidine on Patients with Transient Ventricular Fibrillation, *Am Heart J* 9:792, 1934.

grains (5.82 Gm) have been given repeatedly without untoward result. The necessity for early termination of the attack, especially in patients with extensive underlying heart disease, is obvious, but it must be remembered that the toxic effects of quinidine, such as severe vomiting and conduction disturbances, can be dangerous.

Very favorable results following intravenous administration of the drug have been reported but the danger of severe toxic reactions (vomiting, intraventricular block and standstill with unconsciousness and convulsions) is much greater. Strong and Munroe<sup>30</sup> reported success with intravenous administration of quinidine sulfate to a patient whose condition had been refractory to oral treatment. The attack was stopped only after continuous intravenous administration of 40 grains (2.59 Gm) of quinidine sulfate in a 20 per cent solution, but the patient became unconscious and had an epileptiform convulsion at that point. Hepburn and Rykert<sup>31</sup> reported encouraging results with the intravenous method. In a series of 9 cases, in which 7 patients had had recent myocardial infarction, the attacks stopped in all, and 6 patients were alive for periods up to four years. Only 1 had a severe reaction while receiving quinidine. The results were much better than those obtained by the same authors in another group of 17 patients who did not receive quinidine intravenously, only 3 of whom lived longer than fifteen days. The analysis is not given in sufficient detail, however, to permit a definite conclusion. Hepburn and Rykert prepared a 12 per cent solution for intravenous use by dissolving 60 grains (3.88 Gm) of quinidine sulfate in 500 cc of sterile physiologic solution of sodium chloride or 5 per cent dextrose solution. The solution was then filtered and warmed and given at the rate of 100 to 120 cc, containing 12 to 14 grains (0.8 to 0.9 Gm) of the drug per hour. The average total dose was less than 20 grains (1.3 Gm).

Quinidine was not administered intravenously to any of our patients, although quinine hydrochloride was so used in 1 instance with possible success. The difference between this drug and quinidine is thought to be mostly quantitative, the latter being about twice as strong as quinine hydrochloride.

Patients in whom quinidine given orally is ineffective or cannot be absorbed because of vomiting, and to whom it is considered inadvisable to administer the drug intravenously, may be treated by the intramuscular route. Since there is no preparation of quinidine at present

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30 Strong, G. F., and Munroe, D. S. Paroxysmal Ventricular Tachycardia, with Report of an Unusual Case, *Am Heart J* **19** 486, 1940.

31 Hepburn, J., and Rykert, H. E. The Use of Quinidine Sulfate Intravenously in Ventricular Tachycardia, *Am Heart J* **14** 620, 1937.

# STUDIES ON THE CLINICAL SIGNIFICANCE OF THE SERUM PROTEINS

## II THE RELATIONSHIP BETWEEN THE ALBUMIN-GLOBULIN RATIO, ALBUMIN, GLOBULIN AND TOTAL PROTEIN

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Denis<sup>1</sup> in 1856 was probably the first to report an investigation of the action of various salts on the separation of serum albumin from serum globulin. Hammerstein<sup>2</sup> in 1878 reported the utilization of the precipitating effect of salt for the quantitative estimation of the albumin and the globulin in horse and human serum. In 1882 Burckhardt<sup>3</sup> found that in starving dogs the albumin concentration of the serum fell while the globulin concentration remained stationary. In 1912 Epstein<sup>4</sup> reported that in 12 patients with "nephrosis" the only constant deviation from normal in the serum protein was the lowering of albumin. The absolute globulin level remained essentially constant. He expressed his findings as an albumin-globulin ratio ("A/G ratio"), and since his report this relative method of expression has become deeply rooted in medical literature. It should be noted, however, that when the albumin-globulin ratio is thus reversed, reporting this ratio alone, without reference to the total protein, often (as here) gives one the false impression of a change in the concentration of globulin.

Moore and Van Slyke<sup>5</sup> and others have shown that in certain conditions the albumin concentration of serum is lowered while the globulin concentration remains at a normal level and that therefore the total serum protein value falls in proportion to the drop in albumin concentration. On the other hand, Jeghers and Selesnick<sup>6</sup> found that

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1 Denis, P. S. *Memoire sur le sang*, Paris, J. B. Bailliere & fils, 1859. *Nouvelles études chimiques*, Paris, J. B. Bailliere, 1856.

2 Hammerstein, O. *Ueber das Paraglobulin*, *Arch f d ges Physiol* **17** 413-468, 1878.

3 Burckhardt, A. E. *Beitrage zur Chemie und Physiologie des Blutserums*, *Arch f exper Path u Pharmacol* **16** 322-343, 1882-1883.

4 Epstein, A. A. *A Contribution to the Study of the Chemistry of Blood Serum*, *J Exper Med* **16** 619-731, 1912.

5 Moore, N. S., and Van Slyke, D. D. *The Relationship Between Plasma Specific Gravity, Plasma Protein Content, and Edema in Nephritis*, *J Clin Investigation* **8** 337-355, 1930.

6 Jeghers, H., and Selesnick, S. *Hyperproteinemia Its Significance*, *Internat Clin* **3** 249-280, 1937.



interposed between periods of normal supraventricular conduction. These two types have been arbitrarily designated as "persistent" and "intermittent" tachycardia.

2 In all but 1 case organic heart disease was present, in 28 cases being of the degenerative type.

3 Digitalis intoxication was clearly associated with the attack in 8 instances and was the probable precipitating factor in 9 more. One patient had received large doses of both digitalis and quinidine prior to the onset of the attack. Attacks occurred in association with myocardial infarction 6 times, and in 3 instances myocardial infarction was probably present.

4 Twenty-one patients died in the hospital, 8 in the attack and 12 (all but 1 of the remainder) within a month of its cessation.

5 The occurrence and prognosis of the attacks have also been analyzed in respect to associated electrocardiographic abnormalities and such factors as age, heart rate and width of QRS. The prognosis of paroxysmal ventricular tachycardia is serious, but it is essentially the prognosis of the underlying heart disease present. In our series the prognosis of the "intermittent" type was somewhat better than that of the "persistent" type.

6 The physiologic mechanism involved, the clinical symptomatology, the criteria for the clinical and electrocardiographic diagnosis and the therapy of the attacks with particular reference to quinidine are discussed.

those with advanced cirrhosis. 3 Persistent increases in the total protein concentration above normal have, on the other hand, almost invariably been due to an increase in globulin concentration. 4 Increase in serum albumin content above normal has never previously been reported and seems not to occur except briefly in the early period of dehydration.

In recent years the marked chemical, physiologic and immunologic differences between albumin and globulin have become more clear. The globulin molecule is about two and a half times as large as the albumin. The osmotic influence of the albumin fraction is about four times that of the globulin fraction, and it is of greater importance in the maintenance of blood volume and fluid balance in the body. On the other hand the immune bodies of the blood are principally in the globulin fraction. The albumin fraction is readily affected by the dietary intake of protein, but not the globulin. Globulin is much more quickly regenerated following hemorrhage than is albumin. It is likely, though not yet proved, that serum albumin is formed in the liver by synthesis from amino acids. Less is known of the origin of globulin, but it has been suggested recently by Bing and Plum<sup>10</sup> that the plasma cells of bone marrow and cells belonging to the reticuloendothelial system in and outside the marrow are of importance.

Many investigations have suggested that serum albumin and serum globulin must be considered separately in an evaluation of their clinical significance and that the albumin-globulin ratio alone is unsatisfactory. For example in both nephrosis and venereal lymphogranuloma the albumin-globulin ratio is reversed, however, in the former this is due to a lowering of the serum albumin, and in the latter it is due to an increase in serum globulin.

We are therefore faced with two problems. 1 Is it sufficient to give only the figure for the total protein, and if so, in which cases should this be done? 2 In those cases in which the figure for total protein alone is not sufficient, is it advisable to give the albumin-globulin ratio or would it be clearer and would the determinations be more valuable if the absolute values of the albumin and globulin fractions were presented?

#### ANALYSIS OF DATA

The data represent such a variety of cases as would ordinarily be seen in a large, busy hospital over a two year period. For purposes of study, they fall naturally into two main divisions. The first division consists of cases in which the concentration of the total serum protein was normal or below normal (7.5 Gm per hundred cubic centimeters

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<sup>10</sup> Bing, J., and Plum, P. Serum Proteins in Leucopenia, *Acta med. Scandinav.* 92: 415-428, 1937.

an increase in total serum protein above normal was invariably due to an increase in serum globulin

The present investigation was undertaken in order to clarify further the clinical significance of the relation between these two components of serum protein and to establish a more definite evaluation of the total serum protein. It is proposed also to determine the types of cases in which an accurate determination of serum albumin and serum globulin is informative and those in which it is not. It is hoped thus to eliminate wherever possible the laborious and difficult task of making accurate determinations of albumin and globulin and to show that in those cases in which such determinations are necessary the absolute values of albumin and globulin are essential and the albumin-globulin ratio alone misleading. In all other instances the determination of the total protein by a simple technic, such as the falling drop method,<sup>7</sup> suffices for clinical purposes.

#### MATERIAL AND METHOD

This report is based on 539 determinations of albumin and globulin on specimens of serum obtained from 345 patients in the Johns Hopkins Hospital over the period from November 1935 to September 1937. The data cover a great variety of diseases.

The method used was a macro-Kjeldahl modification of the Howe<sup>8</sup> procedure. The precipitation was done with sodium sulfate by the Howe technic, and the titrations were done with the methyl red-methylene blue indicator described by Johnson and Green.<sup>9</sup> Nonprotein nitrogen was determined by the micro-Kjeldahl method.

#### QUESTIONS RAISED BY THIS STUDY AND A REVIEW OF THE LITERATURE

A study of the material just mentioned as well as of the pertinent literature revealed the following interesting facts. 1. Decreases in total protein concentration below normal have been due almost invariably to decreases in albumin concentration. 2. Globulin concentration below the accepted normal level has been noted only in premature infants, in patients in the early period of severe hemorrhage and occasionally in

7 Kagan, B. M. A Simple Method for the Estimation of Total Protein Content of Plasma and Serum. I. A Falling Drop Method for the Determination of Specific Gravity, *J. Clin. Investigation* **17** 369-372, 1938, II. The Estimation of Total Protein Content of Human Plasma and Serum by the Use of the Falling Drop Method, *ibid.* **17** 372-376, 1938, Studies on the Clinical Significance of the Serum Proteins. I. The Protein Content of Normal Human Venous and Capillary Serum and Factors Affecting the Accuracy of Its Determination, *J. Lab. & Clin. Med.* **27** 1457-1463, 1942.

8 Howe, P. E. Use of Sodium Sulfate as Globulin Precipitant in Determination of Protein of Blood, *J. Biol. Chem.* **49** 93-107, 1921, The Determination of Protein in Blood. A Micromethod, *ibid.* **49** 109-113, 1921.

9 Johnson, A. H., and Green, J. R. Modified Methyl Red and Sodium Alizarin Sulfonate Indicators, *Indust. & Engin. Chem.* **22** 1930.

The correlation equation for the data of this group is  $A = 0.42 \times (TP + 0.34)$ . The coefficient of correlation is 0.4319, and the standard error of estimate is  $\pm 0.7$  Gm per hundred cubic centimeters, or 24 per cent.

The accompanying table gives an analysis of these data. Briefly, 42 per cent of the cases in this group were instances of hepatic involvement, 29 per cent, acute glomerular nephritis with its usual associated infections, 26 per cent, two conditions occurring simultaneously, the one affecting albumin and the other globulin. In 3 per cent, not included in the table, there was severe acute hemorrhage, and in this small group albumin was lowered and globulin also was slightly below normal during the early period of the hemorrhage. In this type of case the con-

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*Conditions Causing Hyperglobulinemia and Hypoalbuminemia Simultaneously*

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1 Hepatic diseases

A Cirrhosis

(a) Primary

(b) Secondary to heart failure

B Carcinoma

(a) Primary

(b) Metastatic

2 Acute glomerular nephritis

3 Combination of two diseases, the one causing an increase of globulin and the other a decrease of albumin, as for example

A Increase of globulin

(a) Syphilis

(b) Tuberculosis

(c) Venereal lymphogranuloma

(d) Periarteritis nodosa

(e) Subacute bacterial endocarditis

(f) Multiple myeloma

B Decrease of albumin

(a) Nephritis

(b) Malnutrition

(c) Diarrhea

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centration of globulin returns to normal quickly, and thereafter changes in total serum protein are related to changes in albumin in a linear fashion, as noted in the first formula given.

*Cases in Which Total Protein Was Above 7.5 Gm per Hundred Cubic Centimeters*—Total serum protein was above 7.5 Gm per hundred cubic centimeters in 9 per cent of the 345 cases studied. In each instance the increase was due to an increase in globulin. This finding and a review of the data in the literature show that total serum protein above 7.5 Gm per hundred cubic centimeters means almost invariably an increase in globulin above normal, a fact which suffices for most clinical purposes. In the majority of cases in which hyperproteinemia occurred there was slight lowering of the apparently more easily affected albumin fraction. Of course, when it is important to know the exact level of albumin in this group of cases, it is necessary to determine it quantitatively. This group of cases will be discussed in more detail in a subsequent paper.

or less) and constitutes 91 per cent of all the cases studied, the second division consists of cases in which there was associated hyperproteinemia (total serum protein above 7.5 Gm per hundred cubic centimeters) and constitutes only 9 per cent of the cases studied

*Cases in Which Total Protein Was 7.5 Gm or Less per Hundred Cubic Centimeters*—In 71 per cent of all the cases in which the concentration of the total serum protein was found to be 7.5 Gm or less per hundred cubic centimeters, only albumin was affected. In 29 per cent both albumin and globulin were changed.

First consideration will be given the larger group—that in which only albumin was affected. In this group globulin remained within normal limits, and a linear relationship was found to exist between total protein and albumin. By application of the method of least squares to the data of this group, the following equation was determined

$$A = 0.93 \times (TP - 2.1)$$

in which  $A$  represents albumin and  $TP$  total protein. The coefficient of correlation ( $r$ ) is 0.9967, and the standard error of estimate is  $\pm 0.4$  Gm per hundred cubic centimeters.

Thus it can be seen that in this first group (71 per cent of the cases in this division) the concentration of albumin can be predicated from that of total protein with a standard error of estimate of less than 10 per cent, in other words, the total protein alone gives sufficient indication for clinical purposes.

The smaller group, in which both albumin and globulin were affected, includes all forms of hepatic disease, whether carcinoma, primary or metastatic, or cirrhosis, primary or secondary to chronic heart failure. It also includes the simultaneous occurrence of two conditions, the one causing hyperglobulinemia, the other hypoalbuminemia—such as syphilis and nephritis, tuberculosis and malnutrition, or venereal lymphogranuloma and diarrhea. Of the nephritides, only acute glomerular nephritis is at all regularly associated with decreased albumin and increased globulin. Here the nephritis probably accounts for the decrease in albumin and the associated infection for the increase in globulin. In all of the types of cases just cited, globulin is increased and albumin decreased. Both albumin and globulin may be decreased below normal in the early stage of severe hemorrhage or in far advanced cirrhosis. It is evident, therefore, that in the conditions which make up this entire group the values of albumin and globulin must be considered individually.

In these conditions globulin varies so much that no linear correlation between albumin and total protein obtains, and obviously there is no correlation between total protein and globulin since albumin varies so much.

Thorough application of this procedure instead of the more usual method of determining albumin and globulin by the relatively inaccurate colorimetric method would enhance the value of serum protein determinations and make it possible to do more of them

#### SUMMARY

The expression of the albumin-globulin ratio without reference to the total serum protein content is misleading and should be discarded. The absolute values for albumin and globulin should be used for more clarity.

In all cases in which the total serum protein content is below 7.5 Gm per hundred cubic centimeters and the patient is known not to be suffering from one of the conditions mentioned in the accompanying table, the albumin level of the serum may be predicted from the total protein level by the formula  $A = 0.93 \times (TP - 2.1)$  with sufficient accuracy for ordinary clinical purposes.

When the concentration of total serum protein is above 7.5 Gm per hundred cubic centimeters, it may safely be assumed that the increase is due to a rise in globulin, but the degree of this rise cannot be predicted. The fact that globulin is increased in any particular case may be helpful in differential diagnosis. Further, it may be helpful to know whether this increase is large or small, otherwise the degree of change in globulin is not helpful in the same sense that the degree of change in albumin is. In view of this, simple tests for the detection of hyperglobulinemia are suggested for most clinical purposes.

In the conditions listed in the table a change in the concentration of total serum protein has no quantitative significance. Here too, however, a concentration below 6.0 Gm per hundred cubic centimeters means a decrease in albumin (although this indicates the amount of decrease only relatively) and a concentration above 7.5 Gm per hundred cubic centimeters indicates an increase in globulin. A normal concentration of total protein (6.0 to 7.5 Gm per hundred cubic centimeters) in this group may be due to a decrease in albumin and an increase in globulin. It is for this group that there is the greatest need for an accurate, simple and rapid method of determining serum albumin and globulin. The most reliable practical technic at the present time remains the Kjeldahl. For rapid results a combination of the falling drop technic with the simple formaldehyde-gel or the globulin precipitation test may also be used here.

If these facts are borne in mind, the much overworked diagnostic laboratories can be spared considerable time, and a clearer interpretation of serum proteins can be obtained.

*The Albumin-Globulin Ratio*—In each of the three groups considered, a certain percentage of the determinations showed a reversed albumin-globulin ratio, 18 per cent in the first group, 54 per cent in the second and 59 per cent in the third. The reversal occurred so frequently that it did not serve to distinguish any particular pathologic entity from any other in which serum proteins were affected. In the first group of cases the ratio was reversed because albumin was lowered—even though globulin was normal. In the second group of cases it was reversed because albumin was lowered and globulin increased. In the third group of cases it was reversed because globulin was so markedly increased that reversal occurred even though albumin was normal or only slightly decreased. It is obvious, therefore, that one can make no practical application of the albumin-globulin ratio without reference to the total protein. Since, then, the significance of the albumin-globulin ratio depends solely on its inference of the absolute values of albumin and globulin, it would be much simpler and more conclusive to refer directly to the absolute values for total serum albumin and total serum globulin.

#### COMMENT

This study suggests that a good procedure for a busy clinical laboratory would be first to determine the total serum protein routinely by a simple, rapid and reliable technic, such as the falling drop method.<sup>11</sup> In the majority of cases the clinician can obtain from this all the information he requires. If, however, the total protein is within the normal limits and the clinician suspects a condition or conditions in which both albumin and globulin may be affected, as discussed (see table), then an accurate determination of the absolute values of albumin and globulin should be done by a reliable technic, such as the Kjeldahl. If the latter cannot be used, the formaldehyde-gel test and the globulin precipitation test are simple and are said to indicate any increase in globulin.<sup>11</sup>

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<sup>11</sup> Recommended technics are as follows. For the formaldehyde-gel test (Bing, J. The Formolgel Reaction and Other Globulin Reactions, *Acta med Scandinav* **91** 336-356, 1937) add 2 drops of 40 per cent solution of formaldehyde to 1 cc of serum and read after three hours' standing at room temperature. If the tube can be inverted without losing its contents, the test is positive. For the globulin precipitation test (Naumann, H. N. Saturation of Serum with CO<sub>2</sub>. A Simple Test for Hyperglobulinemia, *Proc Soc Exper Biol & Med* **39** 377-380, 1938) add 0.1 cc of serum to 1.0 cc of distilled water in a test tube 10 mm wide. Saturate with alveolar air and read after fifteen minutes. If definite cloudiness appears, the concentration of globulin is said to be more than 3.0 Gm per hundred cubic centimeters.

The falling drop principle has been applied for the determination of albumin and globulin, but the necessary precautions are too rigorous for routine use, and since only 27 determinations have been correlated with the results obtained by Kjeldahl technic, this method cannot be recommended at this time. (Barbour, P. H., Jr. The Application of the Falling-Drop Method for Specific Gravity Measurement to the Determination of Serum Albumin, *Yale J Biol & Med* **14** 107-114, 1941.)



Fig 1—Gladys C (case 1)

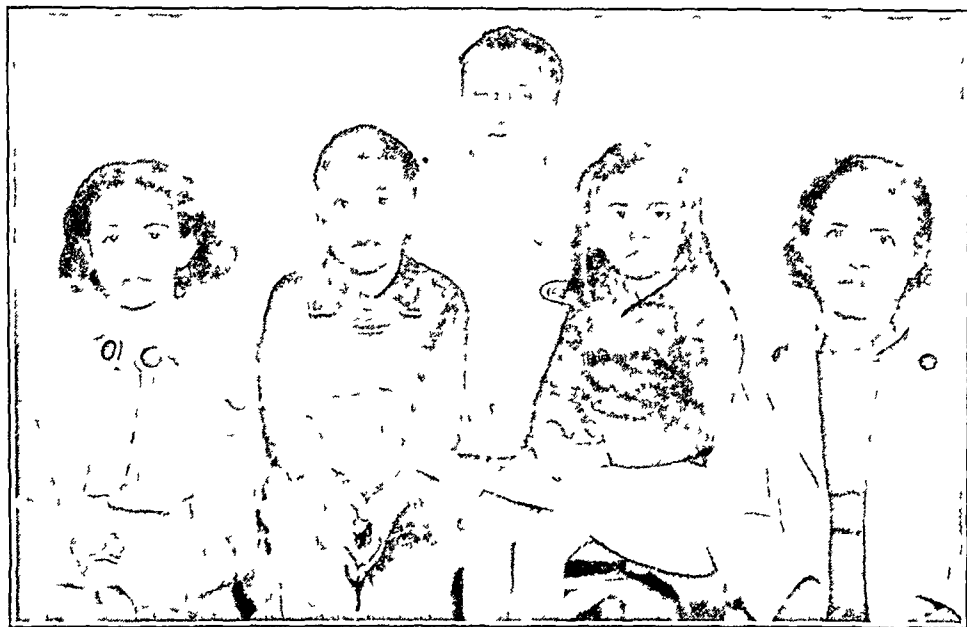


Fig 2—Gladys' family



# SICKLE CELL ANEMIA IN THE WHITE RACE

## WITH REPORT OF CASES IN TWO FAMILIES

M A OGDEN, M D

PASSAIC, N J

In view of the rarity of sickle cell anemia in the white race, 2 cases of this disease in an active form in white families are here presented

### REPORT OF CASES

CASE 1—Gladys C (fig 1), a 9 year old white school girl born of Spanish parentage in New Orleans, came to the outpatient department of the Charity Hospital on May 29, 1939, complaining of pain in the throat. Her tonsils were slightly enlarged and inflamed. Her mother stated that the child often had "head and chest colds" and appeared to be weaker than other children.

She had been delivered normally at term and had weighed 7 pounds (3,175 Gm). On the second day after birth a deep yellow discoloration appeared all over her body. At the age of 3 weeks she was shown to a doctor, who advised the mother not to pay any attention to this condition. At the age of 5 years she had a severe attack of measles.

On Oct 10, 1939, when she again came to the clinic, she appeared deeply jaundiced. According to her parents she had had a yellow discoloration of the whole body all her life. At times it became deeper and at times lighter, but it never disappeared completely. Her scleras had a greenish yellow tint. She was subject to repeated attacks of "sore throat." For the past two years such attacks had been increasing in intensity. She was confined to bed six times during this period and finally had to abandon her studies. Occasionally she had some abdominal discomfort accompanied by diarrhea, but without nausea or vomiting. There was no history of pains in muscles or joints.

*Family History*—Gladys' father and mother were both of Spanish descent and came from Nicaragua to New Orleans, where they had resided for twenty-five years.

The father (fig 2) a 42 year old common laborer, was in good health, and his blood picture was normal. A moist preparation of his whole blood did not show any abnormality in forty-eight hours. The mother (fig 2), a 38 year old factory worker, was slightly anemic and had suffered from "menstrual irregularities" for years. Examination of a direct smear revealed no abnormalities in the blood, but in a moist preparation of her whole blood after forty-eight hours 89 per cent of the erythrocytes became sickled.

A maternal aunt of the patient died at the age of fourteen. Before her death she "turned completely yellow." A paternal aunt of the patient, Victoria C (fig 2), aged 16, was a school girl in good health. Her blood picture, like

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From the Department of Pathology and Bacteriology, Louisiana State University Medical Center, and the Charity Hospital of Louisiana, New Orleans, and the Department of Pathology, Passaic General Hospital.

blood serum The fragility test showed hemolysis beginning at a 0.34 per cent concentration of sodium chloride and complete at a 0.26 per cent concentration The coagulation time was four minutes and the bleeding time five minutes

Examination of a direct blood smear (by my own method)<sup>2</sup> revealed 41 per cent neutrophils, 8 per cent eosinophils, 1 per cent basophils, 42 per cent lymphocytes and 8 per cent monocytes Occasional fragile cells (degenerated leukocytes) were found (fig 4) The Schilling hemogram indicated a slight regenerative shift to the left, with 2 per cent myelocytes, 4 per cent metamyelocytes, 10 per cent band forms and 25 per cent segmented forms among the neutrophils

In a vital staining preparation of 400 leukocytes and 10,000 erythrocytes, 3 per cent normoblasts and 27.5 per cent reticulocytes were encountered and marked basophilic stippling and polychromatophilia were observed Although

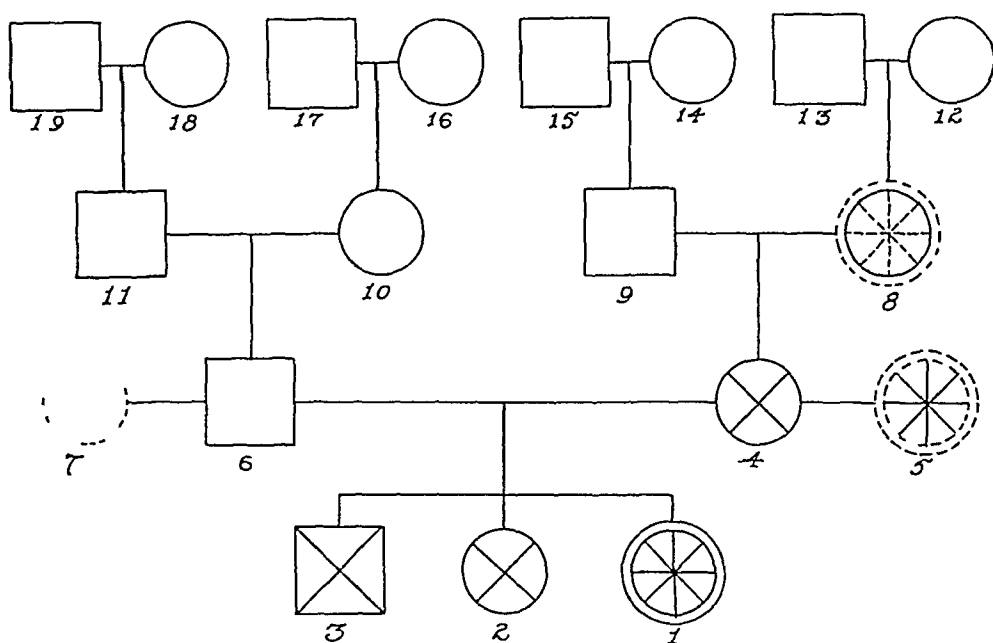


Fig 3 (chart 1)—Family tree of Gladys C. 1 Gladys C, 9 year old patient Sickle cell anemia, active. 2 Mercedes C, 5 year old sister of the patient Sickleemia. 3 Louis C, Jr, 7 year old brother of the patient Sickleemia and anemia. Possibly subclinical type of sickle cell anemia. 4 Mrs Louis C, 38 year old mother of the patient Sickleemia. 5 Maternal aunt of the patient. Died at the age of 14. The history given is suggestive of sickle cell anemia, active. 6 Louis C Sr, 42 year old father of the patient. No blood dyscrasia found. 7 Victoria C, 16 year old paternal aunt of the patient. No blood dyscrasia found. 8 Maternal grandmother of the patient. Died at the age of 35. The history given is suggestive of sickle cell anemia, active. 9, 12, 13, 14 and 15 Maternal ancestors of the patient. 10, 11, 16, 17, 18 and 19 Paternal ancestors of the patient.

about one third of the erythrocytes appeared to be hypochromic, many of them, especially those having sickle and oat shapes, contained an increased amount of

<sup>2</sup> Ogden, M. A. A New Method of Making Smears for Hematologic, Cytologic and Bacteriologic Examinations, *Am J Clin Path (Tech Supp)* 3: 183, 1939.

that of her brother (the father of the patient), was normal both in a direct smear and in a moist preparation after forty-eight hours

The paternal grandfather of the patient died at the age of 73 of rheumatic fever. The paternal grandmother of the patient was 65 and in good health. The paternal great-grandparents, about whose health the patient's father could not give any definite information, came from Spain. The maternal grandparents of the patient had resided all their lives in Nicaragua. The maternal grandmother died at the age of 35. The history of her illness, as related by her daughter, the mother of the patient, is suggestive of active sickle cell anemia. The maternal grandfather was 83 and in good health. The maternal great-grandparents came to Nicaragua from Spain.

The sister of the patient, Mercedes C (fig 2), a 5 year old school girl, appeared to be normal, though slightly undernourished. She had measles at 3. Examination of a direct smear did not reveal any abnormality in the blood. However, after forty-eight hours 81 per cent of the erythrocytes in a moist preparation became sickled. The brother of the patient, Louis C Jr (fig 2), a 7 year old school boy, was slightly anemic. His conjunctivas and labial mucosae were pale, and he was of delicate build. He had had measles at the age of 4 and suffered from occasional headaches and nasal bleedings. His blood picture indicated a slight anemia of normocytic hypochromic type. In a moist preparation of his whole blood 93 per cent of the erythrocytes became sickled after forty-eight hours. In spite of the presence of anemia and sickle-cell anemia in this boy the clinicopathologic complex of the active sickling trait was absent.

*Physical Examination*—Gladys was a poorly nourished, slender white girl weighing 48 pounds (21.8 Kg) (average weight 64 pounds [29.0 Kg]) and 4 feet (121.92 cm) tall (average 4 feet 4 inches [132.08 cm]).<sup>1</sup> The temperature was 99.8 F, the pulse rate 96 and the respiratory rate 20. She appeared to be sufficiently intelligent for her age. No abnormalities were found in her lungs. The heart was slightly enlarged, its right border extended 1 cm to the right of the right parasternal line. The apex beat was in the fifth intercostal space by the left mamillary line. A loud systolic murmur of hemic origin was especially audible at the aortic and mitral valves. The upper and lower extremities were normal, there were no ulcers and no traces of the old, healed scars. The spleen was not felt on palpation and was found to be small on deep percussion. The liver was enlarged, its lower border extended 6 cm below the right costochondral line and was 2 cm above the umbilicus. The gallbladder was not sensitive to pressure, and there was no evidence of general or local lymphadenopathy. Reflexes and systems did not show any noticeable abnormality.

*Laboratory Data*—There were 2,688,000 red blood cells, 11,500 white blood cells and 948,000 platelets per cubic millimeter of blood. The hemoglobin concentration was 49 per cent (7.1 Gm per hundred cubic centimeters), on the 145 Gm = 100 Sahli scale. Hematocrit readings showed 22 volumes per cent of packed erythrocytes. The mean corpuscular volume was 81.5 cubic microns and the mean corpuscular hemoglobin 26.3 micromicrograms. The mean corpuscular hemoglobin concentration was 32.3 per cent, the color index 0.9 and the icterus index 25. The van den Bergh reaction indicated 5.25 units of bilirubin in the

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1 The Average Weight and Height of Children, Tables of the National Child Health Council, cited in *De Re Medicina*, Indianapolis, Eli Lilly & Company, 1941, p. 298.

The urine was clear, gave an acid reaction and had a specific gravity of 1.020. Dextrose was not found, 0.01 per cent of albumin was present, and the reaction for urobilin was positive in a dilution of 1:100. Microscopic examination after centrifugation for five minutes at 500 revolutions per minute revealed 5 to 8 leukocytes per high power field and occasional mucous threads and epithelial cells, but no casts or erythrocytes.



Fig 5—Johnny M (case 2)

Examination of the stool when the patient was on a meat-free diet revealed occult blood (1 plus). Examination of a direct smear, a centrifugal concentration specimen and a zinc sulfate flotation specimen did not reveal any evidence of ova, cysts or parasites.

CASE 2—Johnny M (fig 5), an 8 year old white school boy born in Passaic, N. J., was admitted to the Passaic General Hospital on March 19, 1941 for treatment of "rheumatic fever." He was of German extraction on the paternal side and of mixed Indian (?) and Scotch (?) extraction on the maternal

hemoglobin There were 19 per cent of sickled cells, 6 per cent of oat cells, 3 per cent of ovalocytes and 12 per cent of elongated erythrocytes The remaining erythrocytes were uniconate, polycornate, filiform, monocaudate and bicaudate (caudocytes) There were also some with sharp ends at one or both poles (spiculocytes) and others of indefinite form, some of which were only artefacts

After production of local anaemia (by the method of Scriver and Waugh<sup>3</sup>) examination of a moist preparation of the whole blood by Emmel's method<sup>4</sup> revealed 65 per cent of erythrocytes which sickled immediately Eight per cent had sickled in fifteen minutes, 12 per cent in half an hour, 17 per cent in one hour, 40 per cent in two hours, 55 per cent in three hours, 73 per cent in six

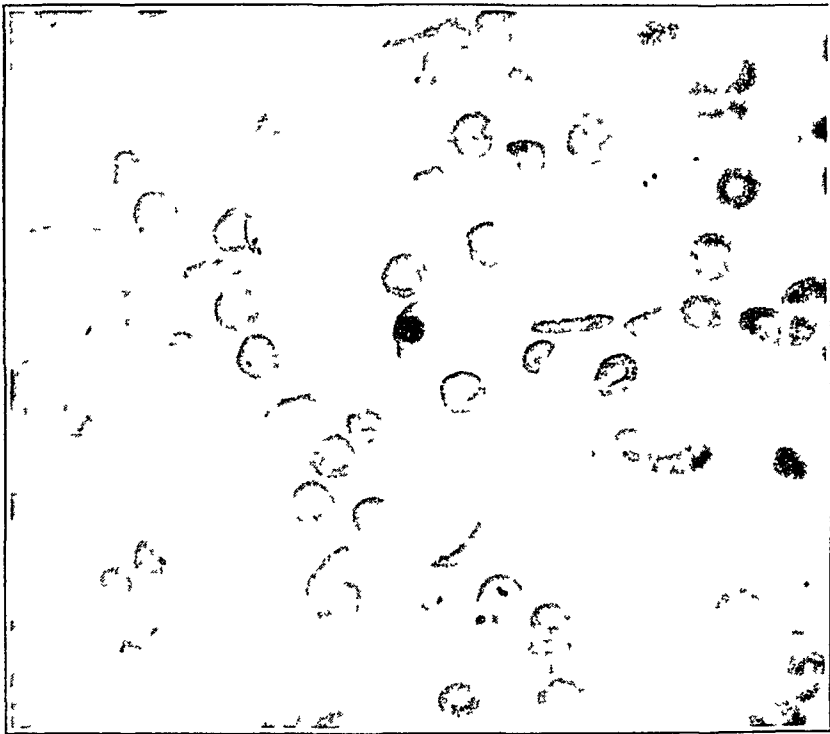


Fig 4—Direct smear of the peripheral blood, Gladys C Drepanoblast and several drepanocytes are observed

hours, 95 per cent in twenty-four hours and 99 per cent in forty-eight hours The blood was kept at room temperature

The blood picture was indicative of severe sickle cell anemia in the active stage and was characterized by leukocytosis, 1 plus, with a slight regenerative shift to the left, erythropenia, 2 plus, with a moderate erythrogenesis, 2 plus, and moderate eosinophilia compatible with sickle cell anemia

3 Scriver, J B, and Waugh, T R Studies on a Case of Sickle-Cell Anemia, *Canad M A J* **23** 375, 1930

4 Emmel, V E A Study of Erythrocytes in a Case of Severe Anemia with Elongated and Sickle-Shaped Red Blood Corpuscles, *Arch Int Med* **20** 586 (Oct) 1917

per cent lymphocytes and 6 per cent monocytes. Among the erythrocytes (fig 6) there were 8 per cent sickle cells, 6 per cent oat cells and occasional cylindrocytes and ovalocytes. In a moist preparation of whole blood 7 per cent of the red blood cells were sickled within fifteen minutes, 36 per cent within fifteen hours and 99 per cent within twenty-four hours.

The sedimentation rate of the red blood cells on March 22, 1941 was one hundred and seventy minutes (Linzenmeier's method). The reaction to the Kahn test of the blood was negative. Examination of culture material from the throat did not reveal diphtheria bacilli or other pathogens.

A specimen of urine taken March 20, 1941 was clear and light amber. The reaction was alkaline and the specific gravity, 1.005. Dextrose and albumin were not found. The reaction for urobilin was positive in a dilution of 1:50. Microscopic examination of the centrifuged sediment revealed occasional degenerated



Fig 6—Direct smear of the peripheral blood, Johnny M

leukocytes and epithelial cells of urinary bladder type, amorphous phosphate, 1 plus, and occasional triple phosphate crystals.

The electrocardiogram showed slight deviation of the axis to the left.

The diagnosis was active sickle cell anemia.

*Family History*—Johnny's father (fig 7), a 40 year old electrician, was born in the Panama Canal Zone and had always been in good health. His blood picture was normal and the erythrocytes in a moist preparation did not show any abnormality after forty-eight hours. Johnny's mother (fig 7), a 34 year old housewife, was born in Buffalo. She was slightly anemic. The red blood cell count was 3,600,000, the hemoglobin concentration 66 per cent (9.1 Gm.), and the white blood cell count 5,100. Examination of a direct smear of her blood did not reveal any noticeable abnormality of the erythrocytic structure except slight anisocytosis. In a moist preparation of the blood 76 per cent of the erythrocytes became sickled within twenty-four hours.

Johnny's eldest brother, Ernest (fig 7), aged 14, had had in childhood an attack of poliomyelitis, which, however, did not cripple him. The red blood

side<sup>5</sup> His mother stated that although he was a full term baby he weighed only 5 pounds (2,268 Gm) at birth, in contrast to her other children, whose average birth weight was 7 pounds (3,175 Gm) In his early childhood he suffered from chickenpox, pertussis and frequent colds Tonsillectomy was performed when he was 3 years old He was always a "sickly" child and suffered from repeated and rather severe "nosebleeds" He went to school, but was compelled by ill health to leave it frequently According to his teacher, he showed little progress in his studies and was considered to be below the average level For the past two years he had suffered from rather severe pains in muscles and joints, especially in the lower extremities These pains were often accompanied by fever He was treated by his family physician for "rheumatic fever" Exposure to ultraviolet radiation and other physical therapeutic procedures were used without success

*Physical Examination*—At the time Johnny entered the hospital he was a pale, anemic-looking, slightly jaundiced, undernourished white child He was so distinctly underdeveloped that no one considered him to be older than 4 years He weighed 37 pounds (16.8 Kg) (average normal, 58 pounds [26.3 Kg]), and his height was 43 inches (109 cm) (average normal, 50 inches [127 cm])

His temperature on admission was 99.8 F, and during his stay in the hospital it showed variations from 98.5 F to 101.4 F (mainly evening elevations) The temperature curve was of the continuous irregular type His pulse rate varied from 80 to 115 and his respiratory rate from 20 to 30

The heart was slightly enlarged, its right border extended 0.5 cm to the right from the right parasternal line A dull systolic murmur of hemic origin was noted

No ulcers or old scars were found either on the upper or on the lower extremities The spleen was not enlarged The liver was moderately enlarged, its lower border being 4 cm below the right costochondral line The gall-bladder was not sensitive to pressure, and no general or local adenopathy was noted

Both knee and ankle joints were painful on moderate pressure, but were not swollen The muscles of both femoral regions were similarly affected

With the aid of roentgenograms slight cardiac hypertrophy was demonstrated Roentgenograms of the skull, arms and legs failed to reveal any evidence of destructive or productive changes in the bones Masses in the mediastinum and active pulmonary lesions could not be demonstrated by means of roentgenograms Reflexes and systems did not show obvious deviation from normal conditions

*Laboratory Data*—The number of red blood cells showed variations from 2,870,000 to 4,490,000 (after blood transfusions), with a hemoglobin concentration of from 45 per cent (6.52 Gm) to 58 per cent (8.41 Gm), on the 13.8 Gm = 100 per cent Sahli scale The number of white blood cells varied from 11,600 to 11,800 Examination of a direct blood smear revealed 71 per cent neutrophils (Schilling hemogram 2 per cent metamyelocytes, 7 per cent band forms, 62 per cent segmented), 5 per cent eosinophils, 1 per cent basophils, 17

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5 For a long time Johnny's mother attempted to conceal her Negro ancestry by making confusing statements concerning the Indian and Scotch ancestry, which apparently constituted only minor branches in her family tree, as is indicated in figure 8 She finally admitted Negro ancestry

Johnny's maternal grandmother, aged 55, had a red cell count of 4,050,000, a hemoglobin concentration of 78 per cent (10.76 Gm) and a white cell count of 8,800 (fig 8). Neither a direct smear nor a moist preparation of the whole blood showed any abnormal erythrocytic morphology. Johnny's maternal aunt, aged 31, did not show any abnormal erythrocytic morphology either in a direct smear or in a moist preparation after a routine forty-eight hour check.

A paternal great-grandfather and a paternal great-grandmother of Johnny were Germans. A paternal great-great-grandfather was of pure German descent. A paternal great-great-grandmother was of mixed German and English extraction. The maternal grandfather died at the age of 24 of "some heart trouble," according to Johnny's maternal grandmother, who was still living with the family. A maternal great-grandmother lived in Charleston, S. C. She was of "half Indian (?) " blood. She died at the age of 80 of "indigestion." Her husband (a maternal great-grandfather of Johnny), who died of "dropsy" (?) at the age of

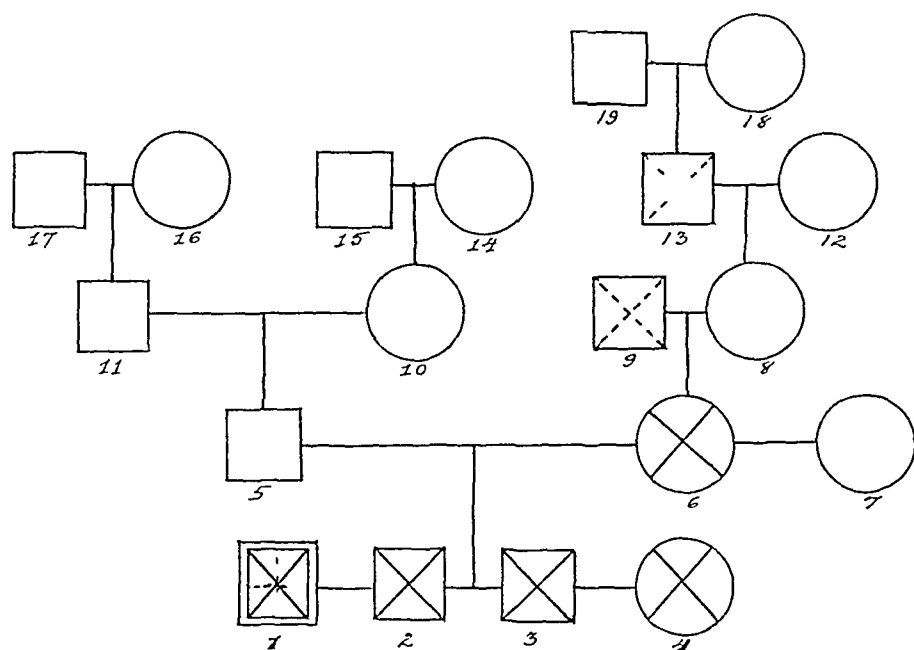


Fig 8 (chart 2) —Family tree of Johnny M. 1 Johnny M, 8 year old white boy Sickle cell anemia, active 2 Ernest M Jr, 14 year old brother of Johnny Sickle cell anemia 3 Joseph M, 10 year old brother of Johnny Sickle cell anemia 4 Joyce M, 19 month old sister of Johnny Sickle cell anemia 5 Ernest M, 40 year old father of Johnny No blood dyscrasia found 6 Mrs Ernest M, 34 year old mother of Johnny Sickle cell anemia 7 Mrs E E, 31 year old maternal aunt of Johnny No blood dyscrasia found 8 Mrs E P, 55 year old maternal grandmother of Johnny No blood dyscrasia found 9 Maternal grandfather of Johnny Died at the age of 24 The history is suggestive of active sickle cell anemia 13 Johnny's maternal great-grandfather, who died at the age of 28 was a Mulatto (1/1) 19 The maternal great-great-grandfather of Johnny was a Negro (sic 1/1) 12 and 18 Maternal ancestors of Johnny 10, 11, 14 15, 16 and 17 Paternal ancestors of Johnny

28, was a mulatto. His father (a maternal great-great-grandfather of Johnny) was a Negro. His mother (a maternal great-great-grandmother of Johnny) was of "mixed" Negro and white blood.

*Blood Grouping of Johnny's Family*—Johnny's father belongs to group A, and his mother to group O. Johnny and his two brothers all belong to group A.



cell count was 4,800,000, the hemoglobin concentration 78 per cent (10.76 Gm) and the white cell count 9,200. Examination of a direct blood smear revealed no abnormal erythrocytic structure. In a moist preparation of the whole blood 88 per cent of the red blood cells became sickled within a twenty-four hour period. Joseph (fig 7), aged 10, another brother of Johnny, had a red cell count of 4,550,000, a hemoglobin concentration of 84 per cent (11.59 Gm) and a white



Fig 7—Johnny's family

cell count of 6,900. Examination of a direct smear of his whole blood revealed no abnormal erythrocytic structure. Ninety-two per cent of the erythrocytes in a moist preparation of whole blood became sickled within twenty-four hours. Joyce (fig 7), Johnny's baby sister, 19 months old, had a red cell count of 3,900,000 and a hemoglobin concentration of 50 per cent (6.9 Gm). Examination of a direct smear revealed slight anisocytosis. In a moist preparation of the whole blood 63 per cent of the erythrocytes became sickled within twenty-four hours.

series only occasional cells became sickled at the end of twenty-four hours. However, at the end of forty-eight hours as many as 23 to 38 per cent of erythrocytes became sickled. The moist preparations were observed for at least forty-eight hours, since if the period of observation is limited to twenty-four hours delayed sickleemia may be missed.

I refer to sickleemia as "immediate" or "delayed" without the use of the word "latent," because although in such patients the typical clinicopathologic complex of the active form is not found, there apparently exists a variety of subclinical types of sickle cell anemia which may be activated or abated by factors not yet well understood. The speed of sickling may be an index of activity of trait only in some cases.

I do not believe that the present state of knowledge of this disease permits any attempt at satisfactory classification. The present study suggests that the sickleemic trait is acquired prenatally and that by the time of birth it appears either in the active form, sickle cell anemia, or in the inactive, sickleemia. In this series I was unable to find a single case of "possible activation" of the sickling trait.

The forms noted in this series were active sickle cell anemia (in the stage of relapse or remission), sickleemia in the subclinical, symptomless stage and sickleemia without severe anemia but with only a few symptoms of the active trait. Whether persons born of sickleemic parents and themselves not showing any sickling trait are capable of producing sickleemic progeny is not yet definitely established. For the purpose of determining the incidence of the sickling trait in the white and Negro races in New Orleans, I studied 1,602 unselected, consecutive cases in the outpatient department of the Charity Hospital at New Orleans from Nov. 7, 1939 through May 2, 1940.

*Methods*—Direct smears of the peripheral blood were made according to my own method.<sup>2</sup> Both the smears and the bone marrow preparations obtained from patients with blood dyscrasias were stained with Wright's stain. Moist preparations of the whole blood were obtained by the method of Emmel.<sup>4</sup> They were kept at room temperature for forty-eight hours. Some preparations were kept for several months, but it was found that forty-eight hours is ample time for study of the erythrocytic structure. Within this length of time such untoward complications as hemolysis, multiplication of bacteria, growth of fungi (since the procedure is not sterile), reversion of the elements to their original shape and autoagglutination, although they do occur, usually are not so extensive as to interfere materially with the carrying out of the test. The moist preparations were observed immediately after the blood had been obtained and at the end of two, six, twenty-four and forty-eight hour intervals. In this way the untoward reactions were noted in time. In Negroes local anoxemia was produced before the blood was obtained

It is interesting that although in this family the mother transferred the sickle-cell trait to all her children, they inherited the father's blood group containing agglutinin A. The most remarkable fact from the anthropologic standpoint is that Johnny scarcely shows any characteristics of the Negro race. His mother has crisp, curly hair and a rather wide, flat nose, thus showing some resemblance to a Negress, although her skin is rather light (fig 7).

#### INVESTIGATION

In this work the manifestations of the sickling trait were classified as sickle cell anemia and sickle-cell trait. The latter was considered to be of two varieties, immediate and delayed, between which no sharp line can be drawn. Sickle cell anemia, an active sickling trait, was defined as a clinicopathologic entity in which sickling of the erythrocytes in a moist preparation takes place either immediately or within a short interval, so that at the end of six hours at least 15 per cent of the erythrocytes are sickled. The presence of sickle or oat cells in varying numbers may also be observed in the direct smear.

The phenomenon of sickling is accompanied by a definite clinicopathologic complex, which, according to the general consensus, has numerous manifestations, including jaundice, hepatomegaly, splenomegaly (or splenic atrophy), severe anemia, urobilinuria, ulcers of the legs, abdominal crises, superficial, regional or generalized lymphadenopathy, arthritic and muscular pains, fever, heart murmurs, thickening of the skull, especially of the parietal bones, osteoporosis and osteosclerosis, especially in the long bones, delayed physical development, weakness and sometimes mongoloid facial features. This familial and hereditary disease is transferred to the offspring according to mendelian law (as Sydenstricker<sup>6</sup> first pointed out). It is of extremely chronic character, and may, as in this case, be of lifetime duration with periods of exacerbation and remission. At some periods and in some patients many symptoms may be absent, but the most constant, I believe, are jaundice (clinical or subclinical) and hepatomegaly in combination with the characteristic blood picture already described.

Immediate sickle-cell trait is characterized by the sickling, immediately or within a short period of time (less than six hours), of over 15 per cent of the erythrocytes in the moist preparation. In the direct smear a few sickle or oat cells may sometimes be observed. This condition may also be accompanied by anemia, but the whole clinicopathologic complex of sickle cell anemia, just described, may be absent.

In delayed sickle-cell trait examination of a direct smear does not reveal any characteristic picture. Sickling of the erythrocytes develops in the moist preparation only after prolonged standing. In some cases in this

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<sup>6</sup> Sydenstricker, V. P. Further Observations on Sickle Cell Anemia, *J. A. M. A.* 83:12 (July 5) 1924.

has been pointed out. As far as the white race is concerned, in 8 cases of active sickle cell anemia (including 2 cases reported here) and 12 cases of sicklemia (including 7 cases reported here), the diagnosis appears to be founded on sufficient data to be considered as proved (table 1). The problem of whether this condition is confined to the Negro race or may occur in members of white and yellow races without admixture of Negro blood is not yet satisfactorily solved. However, it

TABLE 1—Cases of Sickle Cell Anemia in the White Race

Year Re ported	Authors	Patient				Sicklemia in the Family
		Sex and Age	Nationality	Place of Birth	Jaundice—J Spleen—S Liver—L	
1929	Cooley, T B. and Lee, P. <i>Am J Dis Child</i> 38: 103 (July) 1929	M 4	Greek	Detroit	J—present S—enlarged L—not recorded	Mother
1932	Rosenfeld, S., and Pincus, J B. <i>Am J M Sc</i> 184: 674, 1932	M 9	Italian	Brooklyn	J—present S—enlarged L—enlarged	Mother, sister
1934	Cooke, J V., and Mack, J K. <i>J Pediat</i> 5: 601, 1934	M 1	American	St. Louis	J—absent S—enlarged L—enlarged	Father
1934	Cooke and Mack	F 3	American (sister of preceding patient)	St. Louis	J—absent S—not enlarged L—enlarged	Father
1937	Haden, R L., and Evans, F D. <i>Arch Int Med</i> 60: 135 (July) 1937	F 21	Sicilian	Sicily	J—present S—enlarged (re- moved previ- ously) L—not recorded	Brother
1937	Haden and Evans	F 15	Sicilian (sister of preceding patient)	United States	J—present S—enlarged L—enlarged	Brother
1941	Ogden	F 9	Spanish	New Orleans	J—present (severe) S—not enlarged L—enlarged	Mother, brother, sister
1941	Ogden	M 8	German	Passaic, N J	J—present (mild) S—not enlarged L—enlarged	Mother, brother J, brother E, sister

\* Some of the cases, for example those in Clarke's report of 2 cases of sickle cell anemia in a Sicilian family (*Nebraska M J* 18: 376 1933) are not included, since according to the author, the father and son in that family possessed the characteristic appearance of Negroes.

appears to me that I have a right to my strong conviction that the sickling trait is a condition found in the Negro race only and that in all cases in which members of white families have such a trait (in the active or inactive form) an admixture of Negro blood in the immediate, or occasionally even in the remote, ancestry has taken place.

So far, in not a single case has descent been definitely traced far enough back to establish beyond question the white ancestry of the person affected. By referring to table 1 it can be concluded that all white persons with sickle cell anemia reported on up to the present time have been persons of Mediterranean origin (Greeks, Italians,

for the test Both a direct smear and a moist preparation were obtained in each case, a complete blood picture studied and a brief history noted

*Patients*—The patients were from 3 weeks to 88 years old There were 910 white persons (451 male and 459 female) and 692 Negroes (173 male and 519 female) Of the 692 Negroes, 45 (8 male and 37 female) showed a sickling trait Sick cell anemia was found in 7 patients (5 male and 2 female) and sickle cell anemia (immediate and delayed) was found in 38 patients (3 male and 35 female) The incidence of the sickling trait in the Negro race was 6.5 per cent There was not a single case of the sickling trait in the 910 white persons studied

The patients with active sickle cell anemia were distributed according to age as follows first decade 1, second decade 4, third decade 1 and fourth decade 1 It is rather a remarkable observation in this series that of the 37 females showing the sickling trait only 2 (5.4 per cent) had an active sickle cell anemia, whereas of the 7 males with the sickling trait 5 (71.4 per cent) suffered from an active sickle cell anemia

Sickle cell anemia was associated with syphilis in 7 patients (6 female, 1 male) It was associated with pertussis in 1, pregnancy in 1, recurrent carcinoma of the breast in 1, chronic salpingitis in 1, "chronic" appendicitis in 1, excessive menstruation in 1, acute pyelitis (also *Trichuris trichiura* and *Enterobius vermicularis* infection) in 1, acute gastritis in 1, retroflexion of the uterus with cystic ovaries in 1, hypertensive heart disease in 2 and uterine fibroids (leiomyomas) in 2 In none of these conditions accompanied by the sickling trait (sickle cell anemia) did activation (sickle cell anemia) develop, nor was activation of the sickling trait observed in the 14 year old white boy (Ernest M., Johnny's brother, mentioned previously) who had had poliomyelitis in childhood

In the course of this investigation it was found that while studying the sickling trait one should consider other blood dyscrasias in which erythrocytic structure plays an important role The details of this study of closely related blood dyscrasias will be presented shortly in a separate paper

#### COMMENT

According to Killingsworth and Wallace,<sup>7</sup> who surveyed the literature on this subject, the average incidence of the sickling trait in Negroes in the United States is 7 per cent It is possible that in different localities and different countries some variations in the incidence of the sickling trait might be found, but for the study of the comparative incidence of this trait standardization of the criteria for the diagnosis and of the technic is desirable For example, the time of observation of the moist preparations should be not less than forty-eight hours, as

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<sup>7</sup> Killingsworth, W. P., and Wallace, S. A. Sick cell anemia in the Southwest, *South. M. J.* 29: 941, 1936

*of the sickling trait in a white person is a definite proof of admixture of Negro blood in the immediate or remote ancestry* In no case of the sickling trait in a white person reported up to the present time has the possibility of admixture of Negro blood been definitely excluded Since it also has been demonstrated that a simple dominant non-sex-linked mendelian character may be transmitted to the bearer's descendants for over four centuries,<sup>9</sup> and since the sickling trait follows the laws of such a transmission it is evident that if the admixture of Negro blood did not occur in the fourth or fifth generations of Gladys' family it might still have taken place as far back as four or five centuries, even at the time of the Moorish occupation of Spain In this case the disease had been active since the patient's birth During the first nine years of her life she had never been completely free from the clinicopathologic complex The disease was also progressing during the last year that this patient was under my observation

I was unable to find elsewhere in the literature a single proved case of the sickling trait in a person of Spanish descent and therefore believe that the case of sickle cell anemia and the 3 cases of sickle anemia in persons of Spanish ancestry here presented are the first to be reported

A case of the sickling trait in a white person to be acceptable should satisfy at least the following requirements

- 1 Photographs of the affected person or persons, including members of the immediate family, in all cases in which this is possible, should be presented

- 2 The family tree should be studied in detail for the purpose of confirming or rejecting the possibility of the existence of the sickling trait in every member

- 3 A photomicrograph of the direct smear (in the active form) or of the moist preparation at the end of forty-eight hours (or before) should be presented

- 4 The nationality and ancestry of the persons affected should be studied in reference to their residence The history of the race to which the affected person belongs should be considered

- 5 Admixture of Negro blood, if any, should be investigated, and any possibility of Mediterranean ancestry should be considered

As far as the incidence of sickle cell anemia in any race is concerned, it should be admitted that the routine diagnostic procedures are

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<sup>9</sup> Boyd (A Text Book of Pathology, ed 3, Philadelphia, Lea & Febiger, 1938, p 387) cites as an example a case of brachydactyly "transmitted from one of Henry the Sixth's nobles in the fifteenth century to descendants living at the present day, the recently exhumed skeleton of the original earl showed the same bony change"

Sicilians and Spaniards), with the exception of one American family, whose ancestry, however, was not traced sufficiently far back, and one German family (Johnny's), in which I was able to prove Negro ancestry

Every living person, if one goes back twenty-four generations, allowing thirty years to a generation, had in the early thirteenth century 16,713,216 ancestors in the direct line<sup>8</sup> If one considers this fact, it becomes obvious that it is practically impossible to exclude with any degree of certainty the existence of an admixture of Negro blood in some members of the white race (table 2)

Hannibal's invasion of Spain and Italy (218 B C ), the Moorish occupation of southern Spain (711 A D to 1492 A D ), slave trade

TABLE 2—Everybody's Ancestry

	One Living Person Has
First generation (present day)	2 parents
Second generation	4 grandparents
Third generation	8 great-grandparents
Fourth generation	16 great-great-grandparents
Fifth generation	32
Sixth generation	64
Seventh generation	128
Eighth generation	256
Ninth generation	512
Tenth generation	1,024
Eleventh generation	2,048
Twelfth generation	4,096
Thirteenth generation	8,192
Fourteenth generation	16,384
Fifteenth generation	32,768
Sixteenth generation	65,536
Seventeenth generation	131,072
Eighteenth generation	262,144
Nineteenth generation	524,288
Twentieth generation	1,044,576
Twenty first generation	2,089,152
Twenty second generation	4,178,304
Twenty third generation	8,356,608
Twenty fourth generation	16,713,216

with Africa, participation of Negroes in European wars and other historic circumstances brought the Negro race into close contact with the white In the first case reported here the parents of the patient came from Nicaragua, which, according to the latest census, has about 750,000 inhabitants Forty thousand are Indians, 2,000 are foreigners of various nationalities and the remainder are Spaniards Although there are no Negroes in Matagalpa, a small town from which the parents of Gladys came, among the 6,000 residents of Bluefields a number of Negroes are domiciled The great-great-grandparents of Gladys in both the maternal and the paternal lines came from Spain Basing my conclusions on the study of a number of cases of sickling trait, including the 54 cases reported here, I assert, without any hesitation, that *presence*

8 Bloodless Phlebotomist, New York, The Denver Chemical Manufacturing Company, 1936, p 21

cell trait, or sicklemia, there will occur cases of sickle-cell anemia in a ratio estimated to be about 1 to 40 or 50." Sydenstricker<sup>6</sup> gave the ratio of sicklemia to sickle cell anemia as 9:1. Graham and McCarty<sup>12</sup> expressed the opinion that this ratio is rather high. However, in the present series the incidence of active sickle cell anemia among possessors of the sickling trait appears to be still higher, about 17 per cent.

Should the number of persons who manifest an active sickle cell anemia be taken as approximately 15 per cent (a proportion of 1 to 7) which, I believe, is quite close to the actual incidence, then, according to the figures given previously, an army of 135,088 people are doomed to complete extermination either in the first or in the second decade of life. Only a few survive until the third decade and still fewer until the fourth decade or later. It has also been proved that (as in both families here reported on) every sicklemic person is a potential bearer of sickle cell anemia and that, while not showing any marked clinical manifestations of the disease himself, he is capable of transferring it in active form to his progeny. Inter marriages between Negroes and white persons, which at one time were permitted in some states, may therefore directly endanger the white race by the transmission of the sicklemic trait.

#### MEDICOLEGAL SIGNIFICANCE OF THE SICKLEMIC TRAIT

I believe that the presence or absence of the sicklemic trait, because of its high incidence in the Negro race, may be of some service in certain medicolegal procedures, for example, the determination of paternity, as a supplement to the use of present knowledge in the realm of hemagglutinins.

#### SUMMARY

1 Nine examples of the sickling trait (2 of them of active sickle cell anemia) in 2 white families are hereby reported.

2 Familial incidence and hereditary transmission of the sickling trait in the maternal line are established in both these families. The mothers in both families had a delayed sicklemia, which possibly is an inactive, subclinical form of the disease, and each of them had transferred the disease in active form to at least 1 child and sicklemia to all the other children in her family.

3 The incidence of the sickling trait in 1,602 unselected patients of both the white and the Negro race was investigated. The sickling trait was found in 6.5 per cent of the Negroes. There was no instance of

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<sup>12</sup> Graham, G. S., and McCarty, S. H. Sickle Cell (Mimoscytic) Anemia, *South M. J.* **23** 598, 1930.



inadequate Many cases are missed because sickle cell anemia can be diagnosed by examination of the direct smear only in the clinically active periods At times when the patient is in the stage of improvement, only a few sickle cells may be found, chiefly by my method of combined thick and thin smears and especially in the thin half of the slide In the thick smear a few sickle cells, if present, are usually obscured by various non-sickled erythrocytes As a rule, sicklemia is missed if only direct smears are made

The sickling trait, as has been previously pointed out, can be diagnosed mainly by means of the moist preparation, and then only if it is kept not less than forty-eight hours at room temperature I use the moist preparation as a part of the routine procedure for determining the blood count and am convinced that such a procedure should be generally accepted As soon as a greater number of such tests are performed on blood from members of different races, more progress will be attained in determining the racial incidence of this condition

#### SICKLE CELL ANEMIA AS A NATIONAL HEALTH PROBLEM

With the exception of the African continent, the largest number of the Negro population is domiciled in the United States, where, according to the 1940 census, there were 12,865,518 Negroes The number of those having the sickling trait is 900,586, or 7 per cent of the total number<sup>7</sup> These figures, of course, are approximate, but as close to the actual number as it is possible to estimate at the present time The proportion of patients with active sickle cell anemia to the total number of sicklemic persons apparently has never been properly estimated, since in a number of cases active sickle cell anemia was evidently overlooked or diagnosed as some other disease, such as malaria, jaundice of unknown cause or rheumatic fever Many children died in the first few months or even days of life from what appeared to be a deep "jaundice of undetermined origin"

In addition, there is marked confusion in the literature as to the proper meaning and definition of the term "sickle cell anemia" I cannot agree with those who state that sicklemia with anemia equals sickle cell anemia, as might be concluded from previously made definitions Much credit goes to Sydenhacker,<sup>8</sup> Emmel,<sup>4</sup> Diggs and Bibb<sup>10</sup> and a number of other observers who clarified to a considerable extent many aspects of this question

In spite of this the question still remains highly controversial Dale<sup>11</sup> stated "Among those individuals whose blood shows a sickle-

10 Diggs, L W, and Bibb, J The Erythrocyte in Sickle Cell Anemia, J A M A **112** 695 (Feb 25) 1939

11 Dale, G C Sickle-Cell Anemia, South J Med & Surg **99** 14, 1937

# SURGICAL TREATMENT FOR CIRRHOSIS

## PROGNOSIS SUBSEQUENT TO OMENTOPEXY

HORACE B CATES, MD

LOS ANGELES

During the last few years, a fairly large group of patients in the Los Angeles County Hospital who were found to have cirrhosis of the liver has been studied, and some of the results of the study have been published<sup>1</sup>. A phase of the problem involved in the treatment of those patients who have ascites leads to a consideration of surgical procedures. Apparently there is considerable difference of opinion among both internists and surgeons concerning the value of omentopexy as a therapeutic measure for patients who have this condition. It was considered worth while, therefore, to analyze the records of patients found to have cirrhosis and treated medically, giving special attention to the duration of their illness and to their life expectancy, and to compare these findings with those obtained from a study of the records of a similar group of patients who had received surgical treatment for ascites. The records of 5 patients who had had omentopexy done were obtained from a private hospital, all others considered in this study were from the Los Angeles County Hospital. Some recent concepts concerning physiologic changes related to disease of the liver and ascites are considered in the comment.

A brief résumé of previous reports dealing with the results of surgical treatment of patients who had cirrhosis and ascites is in order. The original suggestion of a surgical operation for the treatment of this condition was made by Talma<sup>2</sup> in 1898, but the first successful operation was performed in 1895 by Rutherford Morison,<sup>3</sup> whose patient lived two years following the operation. In 1904 Monprofit<sup>4</sup> tabulated

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1 Cates, H B. Relation of Liver Function to Cirrhosis of the Liver and to Alcoholism, *Arch Int Med* **67** 383-398 (Feb.) 1941

2 Talma, S. Chirurgische Öffnung neuer Seitenbahnen für das Blut der Vena porta, *Berl klin Wchnschr* **35** 833, 1898

3 Drummond, D, and Morison, R. A Case of Ascites Due to Cirrhosis of Liver Cured by Operation, *Brit M J* **2** 728, 1896

4 Monprofit, A. Traitement chirurgical de la cirrhose du foie, *Presse méd* **2** 667-670, 1904, cited by White, S. Surgical Treatment of Ascites Secondary to Vascular Cirrhosis of the Liver, *Brit M J* **2** 1287-1296, 1906

the sickling trait in 910 white persons studied in this series (9 cases reported in this article are not included)

4 The sickling trait is a condition found in the Negro race only, and the finding of such a trait in a member of another race indicates an admixture of Negro blood in the immediate or remote ancestry

5 Of the 9 persons with the sickling trait in white families reported on in this article, 4 are apparently the only persons of Spanish nationality and 5 the only persons of German nationality ever reported in world literature as having this condition

6 The use of moist preparations of the whole blood as a routine procedure in all cases and for patients of all races at the time when routine blood counts are performed is recommended

7 For the purpose of more detailed study of erythrocytic variations in making all routine blood counts my technic for preparing blood smears is recommended

8 Criteria for the diagnosis of the sickling trait in white persons are suggested

9 Sickle cell anemia is a national public health problem, especially in the United States. Intermarriages between Negroes and white persons directly endanger the white race by transmission of the sickling trait, as has been proved in 9 cases here presented. Such intermarriages, therefore, should be prohibited by federal law

10 A consideration of the sickling trait in medicolegal work is hereby proposed

11 Of the 45 Negroes with the sickling trait 54 per cent of the females and 71.4 per cent of the males had an active sickle cell anemia

12 In the first family reported in this article the mother had transferred the sicklemic trait to all her 3 children (to 1 in active form). In the second family the mother had transferred the sicklemic trait to all her 4 children (to 1 in active form). At the same time, the 3 sons inherited their father's blood group (A). Grouping of the blood of baby sister Joyce was not available

syphilis, and gastrointestinal hemorrhage occurred in 37, in some instances as a terminal event. Sixty were jaundiced, and in 24 of these the icteric index was more than 60, in 9 it was more than 100. Ascites was present in 71, or 60 per cent of the group. Serum albumin and globulin were determined in 75 patients. The duration of life from the advent of symptoms regarded as diagnostically important, such as ascites, hemorrhage and jaundice, was noted. Other less relevant disturbances such as diarrhea, loss of weight, peripheral neuritis and delirium tremens, symptoms complained of repeatedly, were disregarded, as they are not necessarily indicative of hepatic disease. The rate at which patients died after the onset of first symptoms definitely related to cirrhosis was as follows: within one month, 26, within two months, 42,

TABLE 1—*Duration of Illness of One Hundred and Seventeen Patients\* with Cirrhosis Treated Without Omentopexy*

1 month	26
1 2 months	16
2 3 months	9
3 6 months	14
6 9 months	12
9 months 1 year	7
1 2 years	15
2 3 years	8
3 4 years	4
4 5 years	2
5 6 years	2
10 years and over	2

\* The intervals represent the time from onset of symptoms of cirrhosis until the patient's death, or to the time of his last interview at the Los Angeles General Hospital.

and within three months, 51, or 44 per cent of the group (table 1). During the first year, 84 died, during the second year 15 and during the third year 8. One hundred and seven, or 91 per cent of the group, died within three years of the onset of symptoms. Two patients lived for ten years after the onset. It is self evident that the type of patient with cirrhosis admitted to this institution has a poor prognosis. However, 40 per cent of this group were free of ascites and in order to make a comparison with a group of patients on whom omentopexy was performed, only those having ascites should be selected. The selection was arbitrarily made as follows: the records of consecutive patients who lived longer than one month following onset of symptoms and who had ascites at one time were analyzed as to duration of life or up to the time when they were last interviewed. This group comprised 53 patients. At the second month 14 patients, or 26 per cent, had dropped out, and at the end of one year 33, or 62 per cent, either were dead or

the reports of 224 patients who had had the operation done and found that 84, or 37.5 per cent, of them had died within one month after the operation. In 70 patients, 31 per cent of the group, ascites subsequently disappeared and hemorrhage did not occur. Results of the Talma-Morison operation on 47 patients were reported by W. J. Mayo<sup>5</sup> in 1924 as being good, but the report contains no follow-up studies of the condition of this group. He considered that relatively slight risk was involved in the operation itself, but that ascites, hemorrhage and frequently edema of the lower extremities of these patients made any surgical operation a very serious procedure. The results of surgical treatment of 26 patients were recorded by W. Hughson,<sup>6</sup> who stated early in his skeptical review that a microscopic examination of a biopsy specimen of the liver is the only method by which an absolute diagnosis of cirrhosis can be made during life. He found the record of but 1 patient for whom the diagnosis had been made in this way. He concluded that surgical treatment of patients who have portal cirrhosis and ascites is without value. He found no evidence which indicated that any particular age, sex, race, period of disease or time of appearance of the ascites offered any particular hope of influence on the results that might be obtained by surgical treatment. The average mortality rate attributed to the Talma-Morison operation by Noetzel<sup>7</sup> is from 20 to 30 per cent and the number of cures 30 per cent, but the last statement is not supported by adequate follow-up records. Grinnell<sup>8</sup> treated 23 patients by performing omentopexy and found that 13 of them, 59 per cent, were unimproved. Six patients, 30 per cent of the total, died postoperatively, and 2, 9 per cent, were said to be free of symptoms.

Results of an analysis of the hospital records of 117 consecutive patients whose condition had been diagnosed as cirrhosis of the liver constitutes the basis of the first portion of the present report. The diagnosis was confirmed in 50 of these patients by examination with the peritoneoscope. Ninety-five, or 81 per cent, died, and of these 75 came to autopsy. Twenty-two were alive when this study was made. Eighty-six were males and 31 were females, and their ages ranged from the first to the eighth decade. According to serologic tests 33 had

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5 Mayo, W. J. The Surgical Treatment of Hepatic Cirrhoses, *Ann Surg* **80** 419-424 (Sept.) 1924.

6 Hughson, W. Portal Cirrhosis with Ascites and Its Surgical Treatment, *Arch Surg* **15** 418-440 (Sept.) 1927.

7 Noetzel, W. Zur Talma-Operation der Leberzirrhose, *Arch f klin Chir* **112** 153-156, 1919.

8 Grinnell, S. Omentopexy in Portal Cirrhosis of the Liver with Ascites, *Ann Surg* **101** 891-901 (March) 1935.

After using this plan of management on a group of 112 patients, Snell<sup>12</sup> reported that the average duration of life after treatment was started was about sixteen months

The prognosis of these patients is improved by the use of a diet high in carbohydrate, supplying adequate protein and supplemented by vitamins After using such a regimen, Patek<sup>13</sup> reported the cases of 4 patients whose general condition improved and whose ascites disappeared Since the publication of a report by Rich and Hamilton<sup>14</sup> I have been treating cirrhotic patients by giving large amounts of brewers' yeast and liver extract parenterally, with promising results

The histories of 2 patients who survived ten years after the onset of cirrhosis are incorporated

#### REPORT OF CASES

**CASE 1—History**—E P, a 65 year old white carpenter, was admitted to the hospital Oct 28, 1938 His first symptoms were noticed in 1928 At that time, after he had taken 49 pills for the treatment of arthritis painless jaundice developed and lasted five or six weeks He had no chills or fever but noted clay-colored stools His abdomen became extensively enlarged and remained so During the last two years, he had also been troubled by an inguinal hernia (on the right side) and an umbilical hernia and was admitted to the Los Angeles County Hospital for herniorrhaphy The past history revealed that he was treated for primary syphilis with mercury in 1900 He had drunk from 10 to 20 glasses of beer a day for twenty years, and had had an occasional glass of whisky, until 1935, three years before his admission to the hospital

**Examination**—Nothing unusual was seen about the head or neck The heart's apex, while in the fifth interspace, was displaced to the anterior axillary line by subdiaphragmatic fluid A harsh systolic murmur was present over the fourth left intercostal space and was transmitted to the axilla The diastolic blood pressure was 135, the systolic pressure, 85 The lungs were essentially normal The abdomen was greatly distended, and the abdominal veins were dilated A "caput medusae" was noted A small umbilical hernia was present Shifting dullness and a fluid wave were demonstrable A large, painful inguinal hernia was present on the right side There was no edema of the extremities

**Laboratory Tests**—The blood count revealed 4,600 red cells per cubic millimeter, with a hemoglobin concentration of 85 per cent (13.6 Gm) The white cells count was 3,800, with a normal differential

There was definite melituria, but no acetonuria The fasting blood sugar was 121 mg per hundred cubic centimeters On Oct 31, 1938, his dextrose tolerance, after the ingestion of 2 Gm of dextrose per kilogram of body weight, was as

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12 Snell, A M Clinical Aspects of Portal Cirrhosis, *Ann Int Med* 5 338-357 (April) 1931

13 Patek, A J Treatment of Alcoholic Cirrhosis of the Liver with High Vitamin Therapy, *Proc Soc Exper Biol & Med* 37 329-330 (Nov) 1937

14 Rich, A R, and Hamilton, J D Experimental Production of Cirrhosis of the Liver by Means of Deficient Diet, *Bull Johns Hopkins Hosp* 66 185-198 (March) 1940

no longer returned to the hospital for examination. At the end of the second year, 6 patients had died and 3 were reported as still living—a total of 9. From two to ten years 6 patients had died and 5 remained alive (table 2). The following conclusions should be emphasized. First the patient in whom ascites develops has, on the whole, a better prognosis than those who have hemorrhage or a deep jaundice without ascites, second, it is obvious that the longer the patient has ascites the more favorable is the prognosis, if energetic medical therapy can be initiated.

It might prove profitable to review the impressions of other clinicians regarding the prognosis of cirrhosis. For instance, in 1892 White<sup>9</sup> stated that in his experience he had never seen a cirrhotic patient with ascites who survived long enough for a second paracentesis to be per-

TABLE 2—*Duration of Life of Patients Having Ascites and No Omentoplexy Who Lived Over One Month*

	Died	Living
1 2 months	5	1
2 3 months	6	2
3 6 months	7	3
7 9 months	5	1
10 12 months	3	
1 2 years	6	3
2 4 years	4	3
5 years	1	1
10 years	1	1

formed. The average duration of life was only two months. However, his contemporary, W. B. Cheadle,<sup>10</sup> saw 23 patients who had cirrhosis and ascites, of whom 4 recovered and 2 were in fair health one year after they were first observed. The difference in results reported by these two observers might be explained by the fact that those of the second group who improved were induced to abstain entirely from alcohol. It was Cheadle's opinion that prompt relief of ascites by paracentesis prolonged the lives of his patients.

Later the mercurial diuretics were used in the treatment of this condition. Rowntree, Keith and Barrier<sup>11</sup> obtained encouraging results by the use of acetarsone, ammonium salts and a high carbohydrate diet.

<sup>9</sup> White, W. H. The Cause and Prognosis of Ascites, *Guy's Hosp. Rep.* 49:1-42, 1892.

<sup>10</sup> Cheadle, W. B., in Discussion in the Prognosis and Treatment of Ascites, *Brit. M. J.* 2:1102-1106, 1892.

<sup>11</sup> Rowntree, L. G., Keith, N. M., and Barrier, C. W. Novasurol in the Treatment of Ascites in Hepatic Disease, *J. A. M. A.* 85:1187-1193 (Oct 17) 1925.

Alcoholic hyalin cannot be definitely identified. There is no fat in the liver cells (fig 1). The diagnosis is hyperplastic nodule in Laennec's cirrhosis."

On Nov 6, 1938 the patient's daily intake of protamine zinc insulin was raised from 10 units to 20 units, and a diet containing 128 Gm of carbohydrate, 63 Gm of protein and 80 Gm of fat was prescribed. With this regimen his urine became free of sugar. Paracentesis was repeated on Nov 27, 1938. Five liters of fluid was removed. The patient steadily improved and was discharged from the hospital on Dec 9, 1938, with directions to have a truss made to support his inguinal hernia.

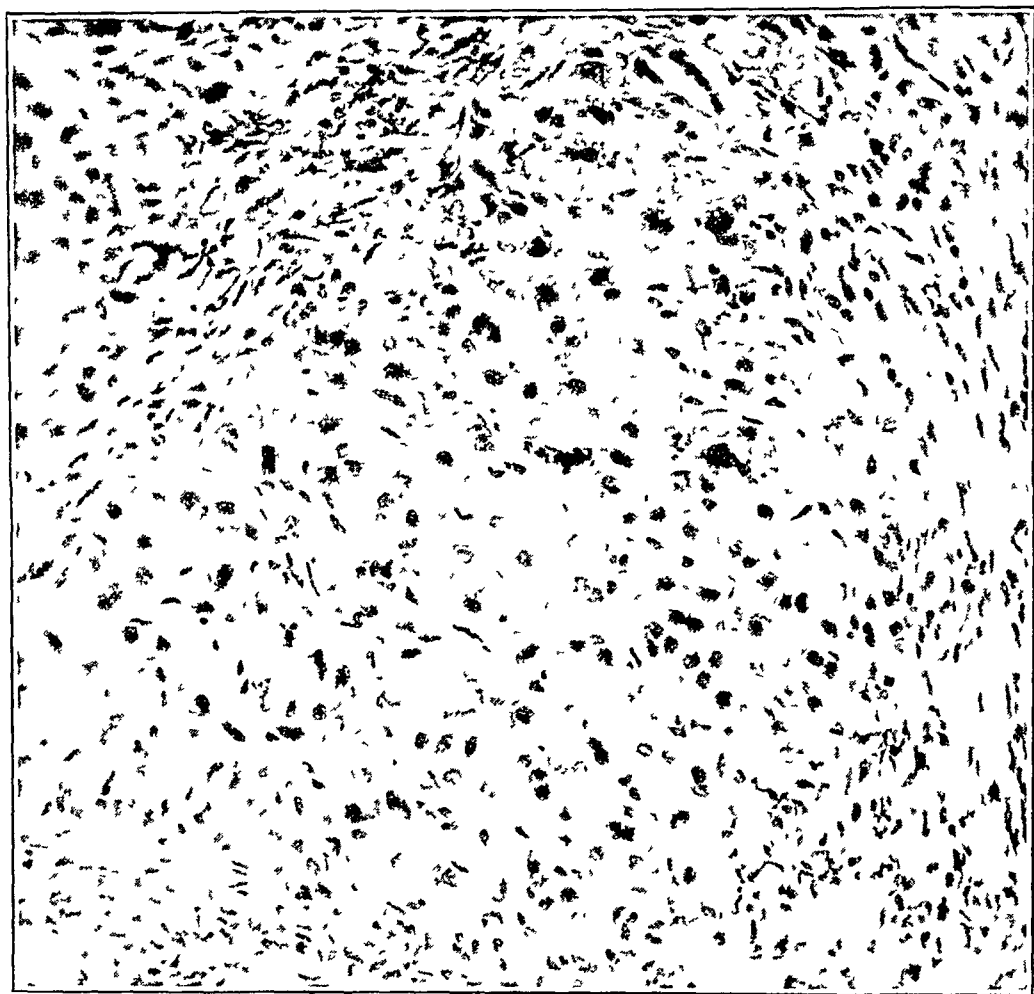


Fig 2 (case 2 [A B])—Slide showing the dilated, bile-stained ducts, marked periportal fibrosis and disturbed cellular structure of the lobules

The patient's initial injury was a severe hepatitis, probably due to cinchophen given for the treatment of arthritis. He had discontinued drinking three years before his admission to this hospital. The diagnosis of diabetes and the use of insulin therapy not only made the urine sugar free but were conducive to hepatic regeneration, ultimately freeing the patient of ascites.

CASE 2—*History*—A B, aged 34, was admitted to the hospital Nov 7, 1938. He was born in Mesopotamia and came to the United States at the age of 22, in 1926. He stated that in 1928 he noticed a fulness and a dragging sensation in



follows first hour, 175 mg per hundred cubic centimeters of blood, second hour, 220 mg, third hour, 263 mg, fourth hour, 308 mg

The result of an echinococcus cutaneous test made on Nov 1, 1938 was reported negative

On Nov 8, 1938 a peritoneoscopic examination was carried out, and 4,000 cc of ascitic fluid was removed Dr John C Ruddock reported as follows "The peritoneal surface was clear The liver was small, shrunk and nodular The spleen was not recognized There was a large right inguinal hernia Conclusion Atrophic cirrhosis"

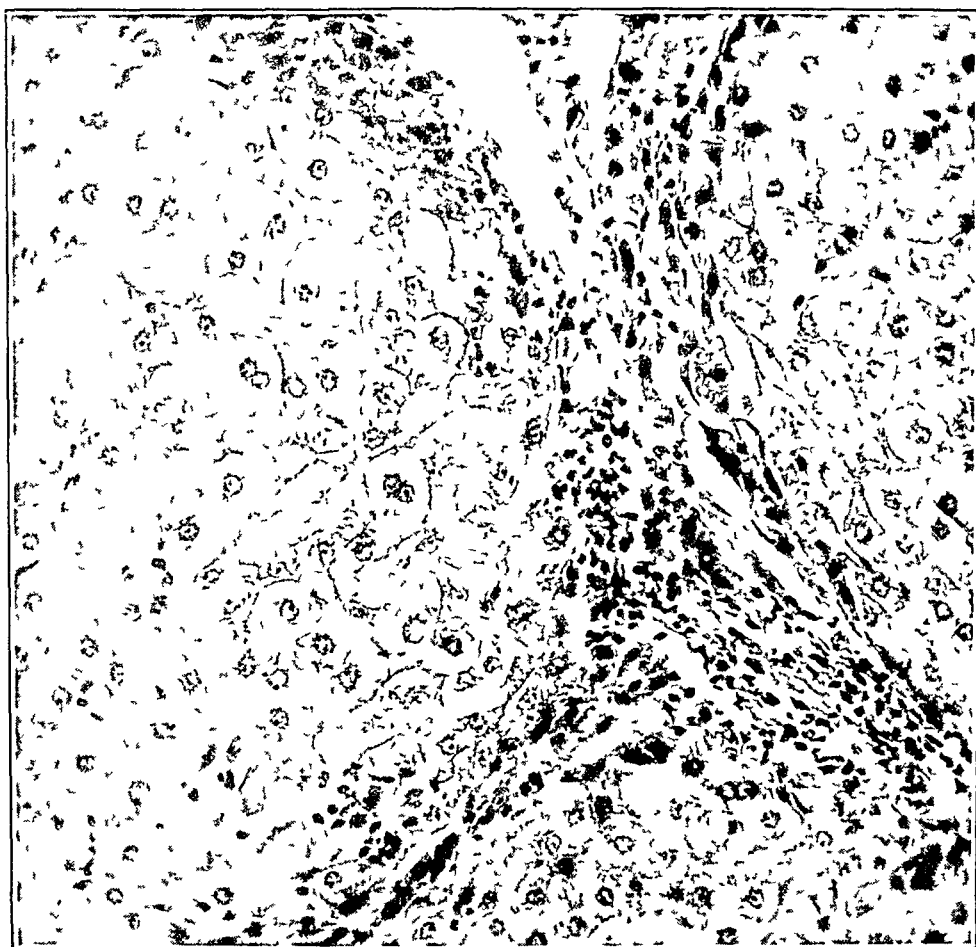


Fig 1 (case 1 [E P]) —Slide showing the increased periportal tissue and disturbance of cellular structure of the lobules

The report on the biopsy of tissue from the liver was reported as follows "The specimen consists of a small portion of liver tissue, measuring 4 by 4 by 3 mm Microscopic examination (paraffin serial sections) reveals that the lobular arrangement is considerably disturbed There is moderate increase in the periportal connective tissue The liver cells are well preserved for the most part Hyperplasia of liver cells is evident in several areas One or two small groups of necrotic liver cells are seen bordering the periportal connective tissue There is moderate round cell infiltration of the latter with no polymorphonuclear leukocytes

moderately infiltrated with round cells Many of the small bile ducts are plugged with bile There is no increase in fat The diagnosis is chronic biliary cirrhosis" (fig 2)

Despite strenuous efforts in treatment the patient remained in a state of shock after the peritoneoscopic examination and died about eighteen hours later

This patient's condition was so critical as to force one to conclude that any form of surgical intervention was contraindicated There was marked elevation of the icterus index and of the total nonprotein nitrogen content of the blood The serum proteins were definitely reduced The sedatives employed are synergistic and must be detoxified by the liver The operation was prolonged, and we now question whether saline solution given intravenously is actually of benefit in combating shock in this type of disease

The total number of patients with ascites (table 3) who were treated by surgical methods was 38 The majority of them were 40 to 60

TABLE 3—*Pertinent Data Concerning Ascitic Patients Subjected to Omentopexy*

Total number of cases (30 males, 8 females)	38					
Total number of patients with alcoholism	21					
Total number of positive Wassermann reactions	13					
Total number having jaundice	21					
Total number of hemorrhages	2					
Peritoneoscopic examinations	24					
Decades of life	2nd	3rd	4th	5th	6th	
	3	5	12	13	5	
Number of patients recorded as living	10					
Number of patients recorded as dead	28					
Postoperative deaths, two weeks	16 (42 per cent)					

years old Twenty-one of this group gave a definite history of alcoholism, but it is our belief that the number of patients with alcoholism was actually higher Thirteen showed serologic evidence of syphilis The incidence of hemorrhage among the group selected by the surgeons was remarkably low, there being only 2 cases, although 21 patients at some time were jaundiced to some degree Peritoneoscopic examinations were made on 24, and on several biopsies of the liver were done at the same time Twenty-eight of those patients are known to be dead Sixteen, or 42 per cent of the group, died within two weeks after having been operated on Of the remaining 12 patients, 10 had died within six months subsequent to the operation, making a total of 68 per cent of the entire series of patients Of the 10 remaining patients, 6 are known to have been alive 6 months after operation One lived 3 years and 11 months For more complete details regarding these patients, particularly regarding the laboratory work which was done, together with the data compiled subsequent to surgical intervention refer to table 4

the abdomen and felt a mass in the upper portion of the abdomen. One year after the onset he became increasingly yellow and turned very dark after exposure to sunshine. The abdominal distention was so distressing that splenectomy was performed in May 1930. His relief was of brief duration, and he was told that his liver was also enlarged. In 1931 he intentionally lost 20 pounds (9 Kg.) by using a special diet, and later he could not recover his former weight. He complained of nocturia, with urination three or four times a night, for five years until four months before his admission to the hospital. His gums had bled at intervals during the last year. The past history was uneventful except for measles and dysentery for one week while a child. He had frequent sore throats. He said he had not had any venereal disease and had never used alcoholic beverages.

*Physical Examination*—Examination revealed a moderately emaciated man with deeply pigmented skin. The temperature was 99.2 F. The pulse rate was 88 and the respiratory rate 20 per minute. There was intense icterus of the scleras. The teeth were poor, and there was retraction of the gums. A few pinpoint hemorrhagic areas were seen. There was slight bulging of the lower part of the right costal margin. Excursion of the chest was poor, and crepitant rales were heard over the base of the right lung. The systolic blood pressure was 104 and the diastolic blood pressure 78. The apical impulse of the heart was visible in the fifth interspace at the midclavicular line, and a thrill was palpated at this point. The mitral first sounds were roughened. There were no cardiac murmurs. The abdomen was moderately distended. There was a midepigastriac surgical scar, and amber fluid oozed from a paracentesis wound in the hypogastrium. Dulness was present in both flanks below the level of the umbilicus. The liver was palpable 4 cm. below the right costal sternal edge, firm and smooth and not tender to pressure. There was moderate scrotal edema.

*Laboratory Tests*—The hemoglobin concentration was 68 per cent. The white blood cell count was 13,500, with normal distribution. The urine gave a 3 plus reaction for urobilinogen and the stool a 1 plus reaction. The fasting sugar content of the blood was 61 mg. per hundred cubic centimeters, the nonprotein nitrogen content 61 mg. and the cholesterol content 143 mg. The serum albumin content was 14 per cent and the serum globulin content 38 per cent. The icterus index was 100 units. The quantitative van den Bergh test indicated 11 mg. of bilirubin per hundred cubic centimeters of blood. The Wassermann reaction of the blood was negative.

Peritoneoscopic examination was done on November 10. Soluble pentobarbital U. S. P. (pentobarbital sodium) and morphine were administered preoperatively. Fifty-five hundred cubic centimeters of bile-stained fluid was removed. Dr. John C. Ruddock reported as follows: "All peritoneal surfaces are clear. The liver is brownish, small, sharp edged and irregular in shape, with multiple black nodules. The edge is curled up, and the left lobe is adherent to the diaphragm with adhesions which are continuous beneath the midline abdominal scar. The gallbladder is distended." Dr. Ernest Hall reported on a biopsy of tissue from the liver as follows: "The specimen consists of tissue from the liver measuring 5 mm. in diameter. Microscopic examination shows a notable disturbance of the normal architecture with considerable fibrosis about the periportal spaces, this being especially apparent about the interlobular bile ducts. Dense bands of fibrous tissue separate the liver cells into nodules of varying size. Some of the nodules are hyperplastic. Many of the liver cells are bile stained. The fibrous tissue is

# *Subjected to Omentopexy*

Other Tests	Operation, Date and Description	Duration of Life After Operation	Peritoneoscopic Examination	Contributory Factors	Autopsy
7/22/35, microscopic examination, extensive cirrhosis, portal type, with fatty changes	7/22/35, liver hard, sclerotic, not typically hobnailed, omentum sutured to posterior sheath of right rectus	1 day	7/6/35 liver nodular, possible syphilitic cirrhosis		7/22/35 Died, no autopsy
8/17/38, galactose tolerance, 14 Gm	10/7/38, omentum split, placed on both sides of incision beneath rectus muscles	2 days			10/9/38 Died, no autopsy
9/14/39, biopsy lymphocytes, ++, polymorphonuclears ++, fat, ++, necrosis, ++, subacute alcoholism, cirrhosis	10/9/39, omentopexy, cholecystectomy no gallstones, omentum spread under surface of recti	2 days	9/14/39, early cirrhosis		10/11/39 Died, no autopsy
6/17/35, hemoglobin 72%, red blood cells, 2,900,000, white blood cells, 28,000	7/8/35, cirrhosis of liver, microscopic section, omentum placed under right rectus muscle spleen 3 times normal size duration 1 hr 10 min, ¼ gram (0.015 Gm) morphine sulfate, 1 cc dial and ethylene	3 days (cholecystectomy, gastric dilatation, acute ileus, secondary)	6/29/35, liver essentially normal, microscopically, multiple hepatic adenoma		7/11/35 Died, no autopsy
5/31/34, microscopic examination, extensive necrotic and fatty changes, inflamed and fibrous proliferation	5/31/34, preoperative diagnosis, possible carcinoma of head of pancreas or cirrhosis, pancreas normal, omentopexy, omentum spread between fascia and subcutaneous fat	3 days		Malaria 20 years previously	6/3/34 Died, no autopsy
	8/21/37, liver moderately enlarged, spleen 4 times normal size, omentum between peritoneum and muscle	4 days	8/7/37, advanced cirrhosis, liver very small, rough, nodular		8/25/37 Died, no autopsy
	7/21/38 (H G S), preoperative diagnosis, obstructive jaundice or biliary cirrhosis, postoperative diagnosis, cirrhosis of liver, splenectomy and omentopexy, pantopon, nitrous oxide and ethylene anesthesia duration 1 hr 15 min	4 days			7/25/38 Died
	5/8/30, omentopexy, liver nodular, hard and small, ether 150 Gm, operation lasted 1 hr 10 min	5 days (H G S)			5/13/30 Died
2/12/38, Takata Ara reaction negative, 2/15/38, Takata Ara reaction +	4/19/38 liver about ½ normal size, spleen 3 times normal size, omentum placed under rectus muscle	5 days	4/10/38, liver small, shrunken, atrophic cirrhosis		4/24/38 Died, liver 1,400 Gm, spleen 850 Gm, cirrhosis severe, anatomic evidence of collateral circulation
	1/15/38, small hobnailed liver, anterior surface of liver traumatized, omentum placed between posterior and anterior sheath of rectus muscle	6 days	11/4/37, atrophic cirrhosis		1/21/38 Died
	11/29/40 (H G S), omentopexy, liver aspirated, liver small, nodular, spinal anesthesia, operation lasted 1 hr 20 min	1 week			11/26/40 Died

TABLE 4—Data on Patients

Patient	Sex	Age	Wasser- mann Reac- tion *	Alco- holism	Date and Onset Before Admission	Ascites	Icteric Index and Van den Bergh Reaction	Protein, Gm per 100 Cc		Hemor- rhage
								Albu- min	Glob- ulin	
1	M	41	0	Alc	6/28/35 1 week, ascites	+	Jaundice, 7/2/35, 53 units, 5 mg			0
2	M	52	0	Alc	8/10/38, 1½ years, ascites	+	8/13/38, 38 units 8/17/38, 36 units, 8/24/38, 20 units, 9/ 6/38, 31 units 9/17/38, 27 units, 9/24/38, 33 units	8/13/38 2 3 3 8/17/38 2 2 9 9/17/38 1 0 3 8 9/24/38 1 7 5 2 5		0
3	F	25	+	Alc (12 glasses of beer daily)	9/10/39 1 month, ascites	+	9/12/39, 20 units			0
4	M	26	0	Alc not heavy	6/15/35 4 weeks	±	6/20/35, 19 units, 12 mg			?
5	M	53	0	Alc	5/7/34 3 weeks	0	5/7/34, 100 units, 175 mg			0
6	M	57	0	Alc	7/24/37, 8 months	+	7/25/37, 20 units	7/25/37 2 3 2 9		
7	M	55	+++		7/1/38 7 months	6 liters	6/29/38, 60 units, 4 mg, 7/ 4/38 52 units 7/ 7/38 62 units, 7/18/38, 73 units			
8	M	56	0		3/18/30, 3 weeks	+	3/29/30, 6 units			+
9	M	32	0	No alc	2/11/38 1 month before ascites	+	2/21/38, 10 units, 3/ 7/38, 7 units	2/15/38 2 8 2 7 3/7/38 3 0 8 2 6		0
10	M	45	0	Alc ?	8/28/37 4 weeks 10/26/37, admission	++++	11/2/37, 10 units			Epistaxis
11	M	46	0	Alc	10/26/40, 3 years, ascites	3 years				

Other Tests	Operation, Date and Description	Duration of Life After Operation	Peritoneoscopic Examination	Contributory Factors	Autopsy
3/21/40, biopsy, necrosis ++, evidence of alcohol ism, hyalin and chronic cirrhosis, 3/4/40, chole- sterol, 176 mg, 38% esters 3/31/40, prothrombin 20%	3/27/40, operation time 69 min, omentopexy, cyclopropane, omentum laid triangularly beneath rectus fascia	1 week	3/20/40, nod- ular, pale, irregular liver, advanced cirrhosis		4/4/40 Died liver 1,890 Gm spleen 530 Gm 3,000 cc fluid generalized peritonitis Laennec's cirrhosis
Hemoglobin, 75%, red blood cells 3 000,000	6/3/35, transverse inci- sion, omentum in split muscles and over perito- neum, spleen not removed	9 days	5/18/35, Banti's disease, strongest possibility		6/12/35 Died liver 950 Gm spleen 1,050 Gm, splenic vein incompletely filled with old antemortem thrombus, diag- nosis portal phlebosclerosis and chronic con- gestive splenomeg- aly and early hepatic cirrhosis portal thrombosis and hepatic necrosis
	7/28/37, omentopexy	2 weeks	3/20/37, small shrunk, gran- ular liver, atrophic cirrhosis		4/7/37 Died no autopsy
	1/7/35 (H G S), omen- topexy, preoperative diagnosis, chronic chole- cystitis, liver twice nor- mal size, acute hepatitis, minimal ascites, opera- tion lasted 29 min	2 weeks			1/21/35 Died no autopsy
	9/10/38, liver smaller than normal, liver trau- matized, omentum at- tached to peritoneum, ether and cyclopropane, operation lasted 1½ hr	2 weeks	8/25/38, small, rough, hobnailed liver, atrophic cirrhosis		9/26/38 Died no autopsy
10/20/39, cholesterol, 63 mg, 39% esters, pro- thrombin 32%, 11/20/39, prothrombin normal 1/25/39, cholesterol, 172 mg, 35% esters	2/2/39, hobnailed, markedly shrunk liver, dome of liver scarified, omentum sutured in muscle and fascia	4 months	11/2/39, cir- rhosis, liver normal size, but small nodules, 12/21/39 char- acteristics of advanced cirrhosis	Typhoid, 11/3/39, biopsy lymphocytes +, necrotic cells +, slight fat, evi- dence of alco- holism, hyalin ++, chronic cirrhosis	4/2/40 Died liver 1,500 Gm spleen 350 Gm portal cir- rhosis with hemorrhage from esoph- ageal vein
	2/24/39, marked cirrho- sis, omentum attached posterior to rectus muscle	7 months	10/1/38, ascitic, nodular, rough and granular liver, atrophic cirrhosis with numerous areas of regeneration		10/9/39 Died no autopsy
	8/10/34, liver somewhat shrunk, left rectus incision peritoneum sutured beneath muscle and subcutaneous tissue	3 years, 8 months	8/6/34, atrophic hobnailed liver		4/14/37 Died liver 800 Gm spleen 600 Gm atrophic cir- rhosis and arteriosclerotic heart disease
	4/29/36, liver shrunk to ½ normal size, nodu- lar, hard, some adhesions at dome of diaphragm, surfaces of liver rough- ened, omentum sutured to anterior abdominal peritoneum	7 weeks	4/18/36, atrophic cirrhosis, gran- ular, irregular wrinkled liver		6/20/36 Died no autopsy

TABLE 4—Data on Patients

Patient	Sex	Age	Wasser mann Reac tion *	Alco holism	Date and Onset Before Admission	Ascites	Icteric Index and Van den Bergh Reaction	Protein, Gm per 100 Cc		Hemor rhage
								Albu min	Glob ulin	
12	M	41	+	Alc (1 gal wine per week and whisky)	2/27/40, 2 weeks	+	4/3/40, 95 units	2/27/40, total protein 6.7 Gm		
13	M	44	0	Alc ?	2 months, ascites before admission, 5/13/35	+	No jaundice			0
14	M	54	+		2/3/37, 6 weeks		2/17/37, 9 units	2/17/37 2.28	2.9	
15	M	47	0	Alc	12/30/34, incidental illness					
16	M	48	+	Alc	8/19/38, 4 weeks		8/21/38, 36 units			+
17	M	30	0	Alc (1 gal beer per week)	10/14/39, 1 month	+	10/11/39, 40 units, jaundice, 3/25/39, 11 units			+
18	M	55	+	Alc	9/10/38, 1 month	—	9/28/38, 12 units	11/18/38 2.9	3.3	0
19	M	67	?		7/14/34, 6 months, ascites, 2/6/37, entered hospital	+	3/25/37, 9 units	3/25/37 2.15	2.2	0
					12/17/34, 20 taps, Preoperative, patient home until 2/6/37, 3/26/37, ascites recurred and patient in coma					
20	F	49	0	Alc, light	4/9/36, 6 months (before ascites)	+	4/9/36, 7.1 units			0

*Subjected to Omentopexy—Continued*

Other Tests	Operation, Date and Description	Duration of Life After Operation	Peritoneoscopic Examination	Contributory Factors	Autopsy
	1/9/37, liver unusually large, not hobnailed, rather roughened, omentum sutured to anterior peritoneum posterior to muscle	5 months		2/9/37, paracentesis, 2/16/37, 4,500 cc, 3/8/37, 2,500 cc	6/8/37 Died, no autopsy
	4/12/32, hobnailed liver, spleen enlarged, omentum sutured outside peritoneum	2 months			6/12/32 Died, no autopsy
	6/6/34, liver hobnailed, portal cirrhosis, omentum brought through peritoneum and laid laterally on it	6 months			12/17/34 Died, jaundice grade 3, hobnailed liver, grade 3 spleen, grade 3 chronic cirrhosis with ascites and jaundice, coroner's case
Bromsulphalein excretion, 27%, galactose tolerance test, no galactosuria	8/16/38 (H G S), omentopexy duration 30 min, spinal anesthesia	10 weeks			10/3/38 Died exploratory laparotomy, ascites 6 liters no pathologic condition found
	5/26/38 omentopexy, omentum placed beneath rectus sheath in fan shaped arrangement, nupercaine, local and spinal anesthesia	1 month 10 days	5/12/38, irregular, nodular, fibrotic liver, capsule thickened, Laennec's cirrhosis and ascites	Tropical dysentery	7/6/38 Died heart 250 Gm, no syphilitic heart disease, omentum, many small vessels traversing anastomosis, parietal peritoneum liver 1,000 Gm, spleen 250 Gm, atrophic cirrhosis, anasarca, subacute peritonitis
	10/6/38, Mayo omentopexy, omentum laid posterior to rectal fascia, in fan shaped arrangement, ether, ethyl chloride anesthesia	Unimproved paracentesis repeated, 4 months	7/30/38, advanced cirrhosis, liver small, nodular		2/11/39 Died no autopsy
	3/14/38, liver, small, atrophic, omentum spread over right rectus sheath into subcutaneous fat, cyclopropane, operation lasted 44 min	7/21/38, not improved, 3 months	2/29/38, atrophic cirrhosis, liver small, wrinkled		7/25/38 Died no autopsy
9/15/38, cholesterol, 177 mg, 60% esters	9/30/38, liver hobnailed ascites, dome roughened, omentum sutured in rectus and subcutaneous tissue, operating time 1 hr, local anesthesia, procaine hydrochloride	2 months			1/13/39 Died coroner, chronic hepatic cirrhosis
9/29/39, microscopic biopsy, occasional necrotic cells, evidence of alcoholism, hyalin $\pm$ , chronic cirrhosis	10/6/39, omentum sutured to edges of peritoneum	12/22/39, no ascites for 7 weeks since operation, 12/22/39, last heard from	9/28/39, hobnailed liver, chronic cirrhosis and ascites		



TABLE 4—Data on Patients

Pa- tient	Sex	Age	Wasser mann Reac- tion *	Alco hollism	Date and Onset Before Admission	Ascites	Icteric Index and Van den Bergh Reaction	Protein, Gm per 100 Cc		Hemor rhage
								Albu min	Glob ulin	
21	M	47	0	Alc	8/20/35, 2 weeks	+ recurring ascites	8/20/35, 26 units, 8/22/35, 20 units, 8/24/35, 10 units, 8/28/35, 9 units, 9/ 8/35, 75 units, 9/12/35, 87 units, 9/24/35, 88 units	8/20/35 3 4 8/28/35 2 8 8/31/35 2 9 9/8/35 3 5 9/14/35 2 8 9/24/35 2 8 8/26/36 3 3 3/10/37 2 9	1 8 1 6 2 1 2 1 2 1 1 8 2 3 2 1	
22	M	68	0	Alc ?	4/14/32, 12 months, ascites before	+	0			0
23	M	54	+	Alc (wine)	5/2/34 6 days before		6 days, jaundice, 5/22/34, 80 units, 5 mg, 5/2/34, 200 units			0
24	F	48			8/7/38, ascites, 2 months		8/9/38, 11 units	8/10/38 2 5	3 0	
25	M	54	++++	Alc	5/3/38, 6 weeks before	+	5/4/38, 15 7 units	5/4/38, 1 16 Gm total protein 5/4/38 2 6/19/38 2 2	2 6 3 8	
26	M	39	+	Alc	7/24/38, 6 months		7/26/38, 14 8 units	8/3/38, total protein 5 8 Gm		
27	M	53	0	Alc	2/12/38 6 days	+				
28	F	62			10/20/37, 6 years	+	12/22/37, 10 units 9/15/38, 60 units, 1/11/39, 87 units	12/22/37 3 1 2/7/38 2 7 9/15/38 3 4	3 6 3 2 3 8	
29	M	48	0	Alc (whisky daily)	9/25/39, 5 months	+	10/2/39, brom sulphalein excre- tion 40%, hippuric acid test, 2 2 Gm, 9/30/39, 5 units	9/29/39 1 8 9/26/39 2	2 4 2 3	

Other Tests	Operation, Date and Description	Duration of Life After Operation	Peritoneoscopic Examination	Contributory Factors	Autopsy
2/15/40, Takata Ara reaction +	4/4/40, liver smooth, slightly enlarged, omentum attached to posterior surface of rectus muscles	12/27/40, still alive, apparently well		11/22/40, ventral hernia	
	4/9/37, trauma of dome of liver, omentum sutured to subcutaneous tissue of abdomen	5/15/40, light work, 8/19/40, patient still alive and in jail	8/24/35, atrophic cirrhosis	Tuberculosis moderately advanced, bilateral, chronic, 10/18/35, from 10/7/36 to 3/26/37 patient had 43 injections of salyrgan, from 5/5/37 to 10/7/37 had 32 injections of mersalyl	
	10/10/36, omentum laid on anterior surface of parietal peritoneum	3/1/38, still alive, 17 months	8/22/36, atrophic cirrhosis	Malaria therapy, 5/7/36, for syphilis of central nervous system, 2/15/37, paracentesis of abdomen, 2,290 cc in toto, thoracentesis, 1,960 cc, 12/26/36, abdominal fluid disappeared hydrothorax occurred after operation	
	4/14/34, hepar lobatum, left rectus incision, omentum placed beneath rectus muscle and remainder under subcutaneous tissue	No return after discharge, 4/30/34	2/17/34 malignant mass involving gall bladder and liver		
1/10/34, microscopic section, mild grade of cirrhosis	5/10/34, omentum spread between muscle and fascia of abdomen	5/13/36, still alive with incisional hernia, still has ascites, 2 years	4/27/34, cirrhosis, atrophic liver		
	7/5/34, liver small, hard, nodular and granular, omentum attached to anterior parietal peritoneum, spinal anesthesia liver 6 times normal size surface dome of liver traumatized	9/19/34, discharged to county farm	4/7/34, cirrhosis, liver atrophic	Paracentesis repeated after operation	
7/26/39, total protein, 7.4 Gm, 12/12/39, total protein, 6.7 Gm, 10/27/39, cholesterol, 135 mg, 35% esters	11/1/39, omentum extensively adherent beneath wound in upper part of abdomen, which caused considerable hemorrhage when abdomen was opened, large plaque of omentum placed under medial rectus flap, operation lasted 1 hr, procaine hydrochloride spinal anesthesia	1/4/40, still alive, 2 months, no very definite effect from omentopexy, 1/12/40, discharged			
	5/20/38, preoperative diagnosis, bleeding gastric lesion, postoperative diagnosis, hemorrhage from esophageal varices 500 cc ascitic fluid, liver ¼ normal size, omentum sutured to inferior rectus sheath, ether	12/19/39, last heard of, 18 months			
12/21/37 Takata Ara reaction —	9/26/38, omentopexy preoperative diagnosis cirrhosis and ascites	9/2/39, still alive, 1 year	4/21/38, peri hepatitis, capsular cirrhosis		

TABLE 4—Data on Patients

Patient	Sex	Age	Wasser- mann Reac- tion *	Alco- holism	Date and Onset Before Admission	Ascites	Icteric Index and Van den Bergh Reaction	Protein, Gm per 100 Cc		Hemor- rhage
								Albu- min	Glob- ulin	
30	F	28	0	No alc	1/29/40, 1 year	+				
31	M	32	—	Alc	7/2/35 1 month	+	7/9/35, 5.5 units	7/9/35, total protein 7.2 Gm		0
32	M	57	+	Alc ?	8/19/36, 1½ months jaundice before	+	6/ 0/36, 20 units	3/12/37 2.5 3.8 2/17/37 2.2 3.3 1/28/37 2 3.5 12/10/36 1.9 3.7 12/1/36 2.1 2.9		0
33	F	61	+		2/2/34 4 months before	—	2/2/34, 12 units			
34	M	53	0	Alc	4/21/34 3 months before	+	4/21/34, 20 units			
35	F	46	+	No alc	4/4/34, 6 months ascites	+	4/4/34, 10.5 units			
36	M	55	0	Alc	7/25/39 1 month	+		10/27/39 2.1 1.9		
						repeated taps since onset				
37	F	64	+	Alc ?	4/20/38, biliary mesitis, 1 day	+				12/3/39 hemor- rhage repeated
38	F	35	0	Alc for 15 years	12/5/37, 9 months, before operation	11/10/38	12/9/37, 26 units 2/ 7/38, 5 units	12/21/37 2.2 2.9 12/23/37 2.5 2.7 2/7/38 2.1 2		

\* In this column, 0 indicates negative reaction

† Pantopon is a mixture of hydrochlorides of opium alkaloids

protein reserves and depressed plasma protein. These fluctuations in volume are considerable. For instance, Lepore<sup>10c</sup> estimated a dog having plasma albumin of 3.82 Gm per hundred cubic centimeters to have a blood volume of 1,414 cc. The plasma albumin was reduced to 2.14 Gm, and the existing blood volume was changed to 1,073 cc. He found a rather constant and direct relationship between the plasma albumin concentration and the plasma volume.

In their studies of secondary traumatic shock, Gasser, Erlanger and Meek<sup>20</sup> stated that diminished blood volume is the only constant factor tending toward failure of circulation. Roome, Keith and Phemister<sup>21</sup> found decreased blood volume when the blood pressure was lowered by hemorrhage, trauma to the extremities or manipulation of the intestines. Under these conditions, with the associated diminished circulating blood volume, the experimental animal is less likely to survive another hemorrhage or operation than to survive other circumstances in which the blood pressure is depressed by shock to a similar degree.

Blalock<sup>22</sup> stated that when rapid hemorrhage occurs there is a diminution in the circulating blood volume, but that because of vasoconstriction the blood pressure is unaltered. If the hemorrhage continues the blood pressure drops in spite of vasoconstriction. Later Minot and Blalock<sup>23</sup> defined shock as a condition due to peripheral vascular failure resulting from a discrepancy between the size of the vascular bed and the volume of circulating blood.

It is maintained that when the plasma proteins, more specifically the albuminous fraction, are reduced to a critical level, edema and a decrease in the circulating blood volume result, and these changes account in part for the high death rate following omentopexy.

Sores and parched tongue are common both in malnutrition and in advanced cirrhosis. Evans and Shulman<sup>24</sup> caution against giving parenterally large amounts of saline fluids to malnourished patients. On account of their hypoproteinemia there is also a disturbance of capillary and extracellular osmotic equilibrium, so that anasarca develops and they have fatal pulmonary edema or eclamptic-like convulsions. However, in those instances in which cirrhosis and ascites are present, the recom-

20 Gasser, H. S., Erlanger, J., and Meek, W. J. Studies in Secondary Traumatic Shock, *Am J Physiol* **50** 31-53 (Oct) 1919.

21 Roome, N. W., Keith, W. S., and Phemister, D. B. Experimental Shock, *Surg, Gynec & Obst* **56** 161-168 (Feb) 1933.

22 Blalock, A. Shock. Further Studies with Particular Reference to the Effects of Hemorrhage, *Arch Surg* **29** 837-857 (Nov) 1934.

23 Minot, A. S., and Blalock, A. Plasma Loss in Severe Dehydration, Shock and Other Conditions as Affected by Therapy, *Ann Surg* **112** 557-567 (Oct) 1940.

24 Evans, J. A., and Shulman, H. On Danger of Forcing Fluids in Malnutrition. *Am J M Sc* **199** 237-246 (Feb) 1940.

## COMMENT

Although the postoperative mortality rate of this group of patients on whom omentopexy was performed is high, it is not correct to maintain that either the skill of the surgeon or the subsequent care of the patient was inferior to that of thirty years ago. Competent surgeons did these omentopexies. The problem involved raises the following questions: Can any form of surgical treatment greatly benefit these patients? Can the disturbance of physiologic function be corrected by mechanical intervention? Are the alterations in the general physiologic status of these patients responsible for the high operative mortality, and if so, how and to what degree can physiologic balance be restored by preoperative management?

The diminution of the serum proteins found in patients who have cirrhosis is responsible for important physiologic readjustments. Tumen and Bockus<sup>15</sup> concluded that hypoalbuminemia was the most constant alteration of the serum proteins. This condition was found at one time or another in all of their patients who had chronic, advanced disease of the liver. Myers and Keefer<sup>16</sup> found a deficiency of total serum protein in 16 patients, and the decrease in albumin was most pronounced. By repeating plasmapheresis on dogs until edema appeared, Weech, Goettsch and Reeves<sup>17</sup> found that their plasma albumin values were below normal. They noted that ascites was invariably present after repeated plasmapheresis, but that edema of the extremities was less intense than when the dogs were subjected to low protein nutritional experiments. Melnick and Cowgill<sup>18</sup> found that the dog, even when subjected to prolonged intensive plasmapheresis for sixteen weeks, shows no impairment of its ability to regenerate plasma proteins. This restorative facility, however, is injured in cirrhosis. Myers and Keefer<sup>16</sup> gave their 4 ascitic patients diets with a high protein content (100 to 300 Gm daily) without success in increasing their levels of blood protein. Investigators<sup>19</sup> pointed out that there is a reduced blood volume coexistent with the depleted

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15 Tumen, H., and Bockus, H. L. The Clinical Significance of Serum Proteins in Hepatic Diseases, *Am J M Sc* **193** 788-800 (June) 1937

16 Myers, W. K., and Keefer, C. S. Relation of Plasma Proteins to Ascites and Edema in Cirrhosis of the Liver, *Arch Int Med* **55** 349-359 (March) 1935

17 Weech, A. A., Goettsch, E., and Reeves, E. B. Nutritional Edema in the Dog, *J Exper Med* **61** 717-734 (May) 1935

18 Melnick, D., and Cowgill, G. R. The Influence of Prolonged Intensive Plasmapheresis upon the Ability of the Organism to Regenerate Serum Protein, *J Exper Med* **66** 493-508 (Oct) 1937

19 (a) Chang, H. C. Plasma Protein and Blood Volume, *Proc Soc Exper Biol & Med* **29** 829-832 (April) 1932. (b) Melnick, D., and Cowgill, G. R. The Serum Protein Complex as a Factor in Regulating Blood Volume, *ibid* **35** 312-314 (Nov) 1936. (c) Lepore, J. Relation of Plasma Volume to Plasma Protein Concentration, *ibid* **30** 268-269 (Dec) 1932

The high mortality rate of the patients who were operated on can be ascribed to undernutrition. It was emphasized that they are more susceptible to shock, that edema of the gastrointestinal organs predisposes to tympanites because of decreased peristalsis and that, in addition, their surgical wounds will not heal normally.

There is, however, another aspect of the condition of patients having cirrhosis and ascites which contraindicates operation. Anesthesia induced by one drug or another naturally is used. Adriani<sup>31</sup> states that anesthetics are detoxified primarily by the liver, although the kidney and other tissues play lesser roles. Nevertheless, the surgeon is prone to neglect this important fact, feeling secure in the idea that the newer techniques of anesthesia are so superior that there is now but a minimal risk.

Mousel and Lundy<sup>32</sup> concluded that, with the possible exception of barbital and phenobarbital, all other hypnotics should be administered with caution. A case is cited, in which afterward the condition was diagnosed as far advanced cirrhosis of the liver, in which pentothal sodium was administered to the patient before peritoneoscopic examination, instead of recovering from the action of the drug in ten minutes he continued to sleep for twenty-four hours. Cameron and de Saram,<sup>33</sup> having produced acute damage of the liver in rats with carbon tetrachloride found them more susceptible to the quickly acting barbiturates. This susceptibility disappeared after hepatic regeneration. They expressed the opinion that the liver's detoxifying functions are impaired even before cirrhosis develops. Pratt<sup>34</sup> established a close correlation between hepatic function as measured by the bromsulphalein test and the prolongation of the action of soluble pentobarbital U. S. P. (pentobarbital sodium). The action of the barbiturates seems also to be intensified when they are administered in conjunction with morphine to healthy rabbits. Vogeler and Kotzoglou<sup>35</sup> gave rabbits morphine salt in quantities of 0.1 mg. per kilogram of body weight and thirty to forty minutes later induced anesthesia with sodium evipal. These rabbits rested ten times as long as those receiving the same amount of sodium evipal without morphine.

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31 Adriani, J. Fate of Anesthetic Drugs in the Body, *Anesthesiology* **1** 312-322 (Nov.) 1940.

32 Mousel, L. H., and Lundy, J. S. Role of the Liver and the Kidneys from the Standpoint of the Anesthetist, *Anesthesiology* **1** 40-55 (July) 1940.

33 Cameron, G. H., and de Saram, G. S. W. The Effect of Liver Damage on the Action of Some Barbiturates, *J. Path. & Bact.* **48** 49-54 (Jan.) 1939.

34 Pratt, T. W., and others. Studies of Liver Function of Dogs, *Am. J. Physiol.* **102** 148-152 (Oct.) 1932.

35 Vogeler, K., and Kotzoglou, P. Administration of Morphine Before Inducing Anesthesia by Sodium Evipal, *Chirurg* **7** 242-245 (April 15) 1935, abstracted, *Internat. S. Digest* **20** 18-20 (July) 1935.

mendations of Collier, Dick and Maddock<sup>25</sup> concerning the control of water exchange in postoperative patients by checking the urinary output are futile, since ascitic patients ordinarily have oliguria. The persistent drainage from the abdominal wound following omentopexy, while beneficial in some respects, further obscures the true status of the patient's water balance. The only measures of value are those which raise and maintain the serum proteins to a normal level. Actually the loss in ascitic fluid of serum and proteins which are utilized for the process of repair further lessens the already depleted reserves. Even with impending edema, Drew, Scudder and Papps,<sup>26</sup> who controlled hydration by means of the hematocrit and determinations of the specific gravity of the blood and of the plasma protein, had no method of adequately rehydrating the blood after surgical procedures.

Symptoms once attributed to portal obstruction, such as nausea, a flatulent type of dyspepsia, constipation and occasional bouts of diarrhea can in part be interpreted as due to dysfunction of the gastrointestinal tract because of the depletion of proteins.

Jones, Eaton and White<sup>27</sup> found that experimental edema involved not only the subcutaneous tissues but all the organs. Proceeding further with the analysis of physiologic disturbances due to the lowering of the plasma proteins to critical levels, Barden, Ravdin and Frazier<sup>28</sup> showed by roentgen studies a marked delay in gastric emptying in both experimental animals and postoperative patients. The gastric emptying time varied inversely with the concentration of plasma protein. Barden and his co-workers<sup>29</sup> found a marked retardation of intestinal motility in dogs in which hypoproteinemia had been produced. Thompson, Ravdin and Frank<sup>30</sup> found that this delay was corrected after the restoration of plasma proteins to normal levels.

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25 Collier, F. A., Dick, V. S., and Maddock, W. G. Maintenance of Normal Water Exchange with Intravenous Fluids, *J. A. M. A.* **107** 1522-1527 (Nov. 7) 1936.

26 Drew, C. R., Scudder, J., and Papps, J. Controlled Fluid with Hematocrit Specific Gravity and Plasma Protein Determination, *Surg., Gynec. & Obst.* **70** 859-867 (May) 1940.

27 Jones, C. M., Eaton, F. B., and White, J. C. Experimental Postoperative Edema, *Arch. Int. Med.* **53** 649-674 (May) 1934.

28 Barden, R. P., Ravdin, I. S., and Frazier, W. D. Hypoproteinemia as a Factor in the Retardation of Gastric Emptying After Operations of the Billroth I or II Types, *Am. J. Roentgenol.* **38** 196-202 (July) 1937.

29 Barden, R. P., Thompson, W. D., Ravdin, I. S., and Frank, I. L. Influence of Serum Protein on the Motility of the Small Intestine, *Surg., Gynec. & Obst.* **66** 819-821 (May) 1938.

30 Thompson, W. D., Ravdin, I. S., and Frank, I. L. Effect of Hypoproteinemia on Wound Disruption, *Arch. Surg.* **36** 500-508 (March) 1938. Thompson, W. D., Ravdin, I. S., Rhoads, J. E., and Frank, I. L. Use of Lyophile Plasma in Correction of Hypoproteinemia and Prevention of Wound Disruption *ibid.* **36** 509-518 (March) 1938.

group had ascites and in addition had survived one month after the onset of symptoms. This entire group was treated medically, and 38 per cent of them lived more than one year.

The total number of patients on whom omentopexy was performed for the relief and cure of ascites was 38, and of these 16, or 42 per cent, died within two weeks after the operation. Follow-up study of the remaining patients leads us to conclude that their prognosis is no more satisfactory than it would have been if medical treatment alone had been given.

In the light of the present concept of the formation of ascites the surgical concept that restoration of collateral circulation from the portal system is possibly by mechanical means is false. Only with a sustained elevation of the vascular osmotic pressure will ascites subside, and this, unfortunately, is not as easily achieved in the patient who has cirrhosis as it is in one who has the edema and ascites associated with degenerative nephritis or nephrosis.

The hypoproteinemia of cirrhosis causes important physiologic alterations, all of which are inimical to surgical intervention. The patient is more susceptible to shock, the restoration of fluids subsequent to operation is fraught with serious risk, wound healing is impaired, and the proper administration of any anesthetic is associated with a greater than average danger.

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A comparative study of tests of hepatic function on patients known to have cirrhosis has recently been made at the Los Angeles General Hospital<sup>1</sup>. It would be conservative to say that this group of patients, particularly those who had ascites, had poor hepatic function. Dunlop<sup>36</sup> concluded with regard to the toxicity of procaine that it is inadvisable to use it on patients having severe disease of the liver. He expressed the belief that the liver is not essential for the detoxification of procaine but that it does detoxify procaine more rapidly and efficiently than do other tissues. Even local anesthesia therefore has contraindications in the simple operation of omentopexy.

When portal ascites develops, water metabolism is altered. Many of the factors contributing to diuresis in nephrosis are operative also in patients who have cirrhosis and ascites. It has been accepted that the liver is responsible for the destruction of the short-acting barbiturates and that the barbiturates with more prolonged action, such as barbital and phenobarbital, are excreted by the kidneys. For instance, after bilateral nephrectomy in rabbits, Hirschfelder and Haury<sup>37</sup> found that the depression due to barbital or phenobarbital persisted until death, whereas the shorter-acting barbiturates had little effect. Murphy and Koppanyi<sup>38</sup> produced acute renal lesions in dogs and rabbits with tartaric acid, potassium chromate and uranium acetate. After the administration of barbital to these nephrotic animals there was a reduced concentration of barbital in the urine and a retention of the drug in the blood and tissues. When barbital was given in anesthetic doses the animals failed to survive. Richards and Appel<sup>39</sup> confirmed that when damage to the liver is produced by chloroform or carbon tetrachloride the action of the long-acting barbital is not affected, but there is a marked prolongation of the effect of the shorter-acting group of barbiturates, such as pentobarbital.

#### CONCLUSION

The prognosis of the patient with cirrhosis seen in this institution is usually poor. Omentopexy performed on selected patients has not prolonged life. The total number of patients in the group who were not treated surgically was 117, and 72 per cent of these patients had died within one year after the onset of symptoms. Fifty-three of this

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36 Dunlop, J. G. The Fate of Procaine in the Dog, *J. Pharmacol. & Exper. Therap.* **55** 464-481 (Dec.) 1935.

37 Hirschfelder, A. D., and Haury, V. G. Effect of Nephrectomy on Duration of Action of Barbitals, *Proc. Soc. Exper. Biol. & Med.* **30** 1059-1060 (May) 1933.

38 Murphy, W. S., and Koppanyi, T. Studies on Barbiturates, *J. Pharmacol. & Exper. Therap.* **52** 70-77 (Sept.) 1934.

39 Richards, R. K., and Appel, M. The Barbiturates and the Liver, *Anesth. & Analg.* **20** 64-77 (March-April) 1941.

# REPORT OF CLINICAL EXPERIMENT

*Clinical Details*—R G, a Puerto Rican man aged 20, was admitted to Sea View Hospital on March 5, 1940, with pulmonary tuberculosis. There were caseous pneumonic involvement of the entire left lung and a productive lesion in the apex of the right lung (fig 1). Tuberculosis had been discovered in 1936. In 1936 and 1937 pneumothorax had been induced on each side for several months, and thoracoscopy had also been performed on the left side. There was no history of rheumatic fever, syphilis, hypertension or any cardiovascular symptoms.

Throughout about two years' observation the patient was ambulatory. The general nutrition improved, and the sputum, which had been positive for tubercle bacilli on admission, became negative for such organisms. Examination showed that the heart was displaced to the left, but there was no evidence of cardiac enlargement or of cardiac insufficiency. A pleuropericardial friction rub was heard



Fig 1—A roentgenogram of chest taken on admission. Note the caseous pneumonic involvement of the left lung and a productive lesion in the apex of the right lung, with marked displacement of the heart to the left.

on one occasion. Blood pressure readings fluctuated, the highest was 190 systolic and 90 diastolic, obtained when the patient was first seen, frequently readings of about 130 systolic and 80 diastolic were noted. The radial arteries were barely palpable, and the dorsal pedal arteries were thickened.

The electrocardiogram taken shortly after admission (March 18) showed a short PR interval (0.09 second), abnormal QRS complexes, with a duration of 0.08 to 0.09 second, and abnormal RT segments (fig 2 A).

The second electrocardiogram, taken one month later (April 15), showed a normal record (fig 2 B). On the same day tracings were taken with the patient in several positions and during different phases of respiration: left lateral position, right lateral position and the sitting position, each during both deep inspiration and deep expiration. The only change obtained by varying the conditions in this way was in the height of the R wave in lead I, which was totally abolished in the left lateral position both in deep inspiration and in deep expiration and to a lesser

# ACTION OF DIGITALIS ON CONDUCTION IN THE SYNDROME OF SHORT PR INTERVAL AND PROLONGED QRS COMPLEX

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AND

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It is stated that the effect of digitalis on the heart can simulate almost every type of electrocardiographic abnormality due to cardiac disorders with the exception of intraventricular conduction defects.<sup>1</sup> As far as the normal electrocardiogram is concerned, this statement is undoubtedly true. The observations of Hart,<sup>2</sup> however, have been widely cited in the literature as indicating that digitalis may occasionally cause a delay in intraventricular conduction and a consequent widening of the QRS complex.

In this study prolongation of the QRS time was produced by digitalis in the course of a clinical experiment. The observations were made in a case of so-called "bundle branch block with short PR interval," a syndrome first observed by Wilson<sup>3</sup> and subsequently described by Wolff, Parkinson and White.<sup>4</sup> Bishop<sup>5</sup> more recently reviewed 45 cases of this syndrome reported in the literature, but as far as we are able to ascertain, the effect of digitalis on this conduction abnormality has not been investigated.

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From the Cardiac Service, Sea View Hospital, and the Department of Pharmacology, Cornell University Medical College

1 Goodman, L., and Gilman, A. The Pharmacological Basis of Therapeutics, New York, The Macmillan Company, 1941, p. 518

2 Hart, T. S. Block of the Branches of the Bundle of His, Arch Int Med **35** 115 (Jan.) 1925

3 Wilson, F. N. A Case in Which the Vagus Influenced the Form of the Ventricular Complex of the Electrocardiogram, Arch Int Med **16** 1008 (Dec.) 1915

4 Wolff, L., Parkinson, J., and White, P. D. Bundle-Branch Block with Short P-R Interval in Healthy Young People Prone to Paroxysmal Tachycardia, Am Heart J **5** 685 (Aug.) 1930

5 Bishop, L. F. Bundle Branch Block with Short P-R Interval in Individuals Without Organic Heart Disease, Am J M Sc **194** 794 (Dec.) 1937

experiment a dose of 0.4 Gm of digitalis was given orally on each of three successive days and a tracing (fig 3C) taken on the fourth day (June 3, 1940). At this time the heart rate was slower than in the control records taken before the administration of digitalis (fig 3A). Marked widening of the QRS complex had appeared, after medication with digitalis it was 0.14 second, whereas in the control tracing it was about 0.10 second. The QT interval increased from 0.36 second in the control record to 0.44 second in that taken after medication with digitalis (lead II). This is contrary to observations on the effect of digitalis on the QT interval in regular sinus rhythm.<sup>6</sup>

Three weeks later, after elimination of the drug, the tracing had returned to the appearance of the previous control record. The experiment was then repeated, and a record similar to that in figure 3C was obtained (July 1). Marked prolongation of QRS time by digitalis was observed in two subsequent experiments (fig 4A). In one of these immediately after a control tracing a single digitalizing dose of digitoxin, 1.25 mg, was given orally and a tracing taken twenty-four

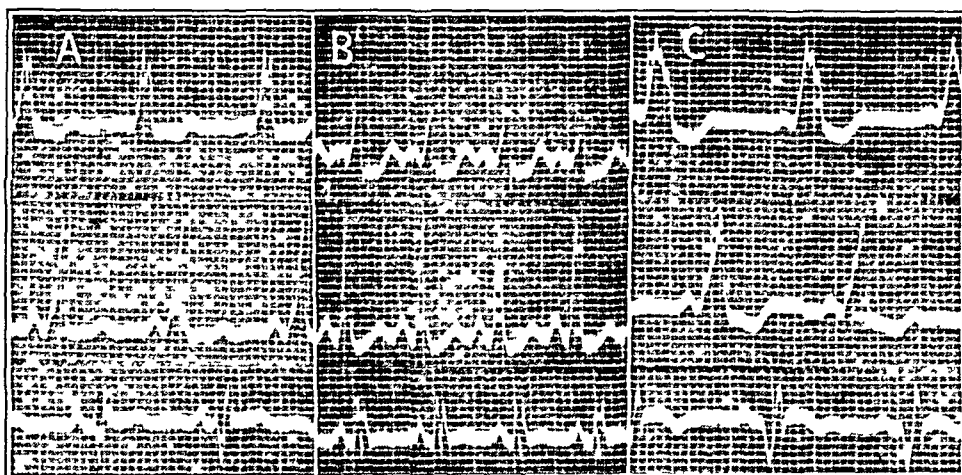


Fig 3—The effect of atropine sulfate and of digitalis on the electrocardiographic abnormalities. A, the control tracing (May 31, 1940) taken just before the administration of atropine sulfate. B, the tracing taken a few minutes after intravenous injection of 2 mg of atropine sulfate. Note the acceleration of the heart rate from 100 to 150 per minute and decrease in the QRS time from 0.10 to 0.07 second. C, the tracing taken on the fourth day (June 3) after beginning administration of digitalis (total dose 18 grains [1.16 Gm] given orally). Note the slowing of the heart rate from 90 in the control record (A) to 70 per minute and widening of the QRS complex to 0.14 second per minute.

hours later. The same effect was observed after the administration of the purified glycoside as after medication with digitalis leaf. Thus, pronounced widening of the QRS complex was produced on each of the four occasions on which digitalis was administered.

6 Cheer, S. N., and Dieuaide, F. R. Studies on the Electrical Systole ("Q-T" Interval) of the Heart. IV. The Effect of Digitalis on Its Duration in Cardiac Failure, *J. Clin. Investigation* **11**: 1241 (Nov.) 1932.

extent was influenced in other positions. The original abnormal tracing was not reproduced. It seemed likely, therefore, that the abnormal rhythm was not the result of mediastinal torsion or displacement.

A tracing taken ten days later (April 25) again showed a short PR interval with abnormal QRS complexes, which differed from the first one in that a notch had appeared on the upstroke of the R wave in lead I near its apex, the R wave in lead II was slurred along the entire upstroke and in lead IV the T wave was positive and there was a reduction in the height of the R wave and a deepening of the S wave. The QRS time was 0.10 second (heart rate 110 per minute). At this time the taking of tracings during deep inspiration and deep expiration (sitting position only) did not introduce any modification of the record.

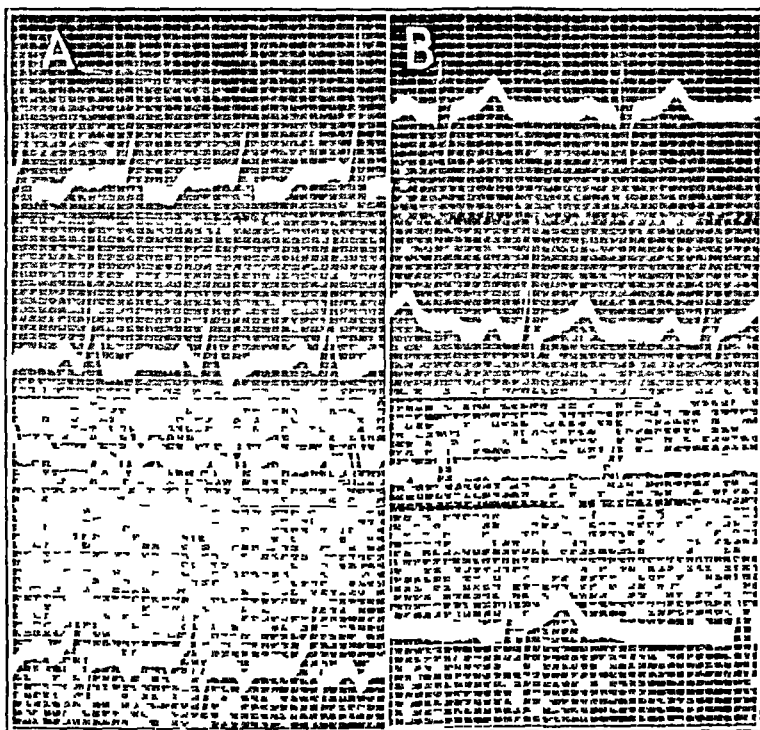


Fig 2—*A*, an electrocardiogram taken shortly after admission. Note that the PR interval is 0.09 second and the abnormal QRS complex has a duration of not exceeding 0.09 second. *B*, a tracing taken one month later, showing a normal sinus rhythm. The PR interval measures 0.17 second, and the QRS complexes are normal.

Over ninety electrocardiograms were taken between March 18, 1940 and Jan 8, 1942. With the exception of the normal tracings obtained on April 15 all showed essentially the same characteristics (figs 2 *A* and 3 *A*). The QRS time, however, showed a tendency in the later tracings to become prolonged to 0.11 or 0.12 second (fig 7 *A*).

Several experiments were carried out to determine the effect on the electrocardiogram of changes in vagal tone produced in various ways.

*Increased Activity of the Vagus Nerve*—Digitalis. The effect of digitalis on the electrocardiographic syndrome was studied in four experiments. In the first

ventricular type of nodal rhythm (fig 5), and the QRS complex now resembled that of the normal sinus rhythm (fig 2*B*). Eight minutes after administration of atropine the tracing had returned to the abnormal form seen in the tracing taken shortly after admission.

Four and a half months later (April 11, 1941) the mecholyl chloride-atropine sulfate experiment was repeated (fig 6). This time a larger dose of mecholyl chloride, 25 mg, was given subcutaneously. The control blood pressure reading

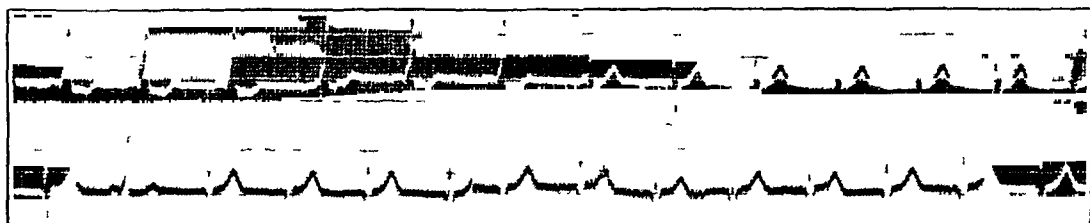


Fig 5—The effect of atropine sulfate after the administration of mecholyl chloride (15 mg), first experiment (lead I). Sections have been selected from a continuous tracing taken immediately after the intravenous injection of 12 mg of atropine sulfate. Note the transition of the electrocardiographic abnormalities to a supraventricular nodal rhythm, with occasional escape to the abnormal form, and occasional appearance of an M-shaped complex.

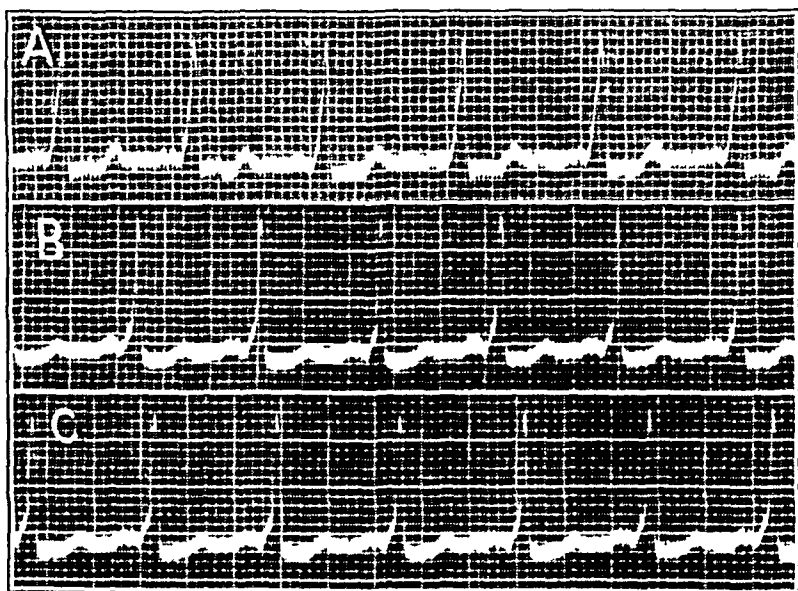


Fig 6—The effect of atropine sulfate after the administration of mecholyl chloride (25 mg), second experiment (lead I). *A*, the control record; *B*, a tracing illustrating the effect of mecholyl chloride. Note that the only changes are a slight increase in rate and more pronounced notching of the P wave; *C*, the tracing taken a few minutes after intravenous injection of 2 mg of atropine sulfate. The record is the same as that taken after the administration of mecholyl chloride.

was 142 systolic and 80 diastolic. Four minutes after administration of mecholyl chloride it was 134 systolic and 66 diastolic; the patient was flushed, lacrinating and perspiring profusely. Tracings were taken for twelve minutes after the injection. There was no change in the PR interval or in the configuration of the QRS complex (fig 6*B*). Atropine sulfate 2 mg, was then injected intravenously.

An arrhythmia (fig 4 *C*) similar to sinus arrhythmia was frequently seen in the tracings after medication with digitalis

On December 6, when marked widening of the QRS time was in evidence after the administration of digitalis (fig 4 *A*), atropine sulfate, 12 mg, was given intravenously. The immediate effect (fig 4 *B*) was an increase in heart rate and a decrease in the QRS time to 0.07 second from the previous value of about 0.14 second. Twenty-four hours later the digitalis effect had reappeared (fig 4 *C*). At this time the arrhythmia was most distinct. The results of this experiment suggest that the digitalis effect on the QRS complex is vagal in origin.

**Pressure on the Carotid Sinus.** Pressure on the right and the left carotid sinus had no effect on the electrocardiographic changes (November 29). At this time the control record showed a QRS time of 0.09 to 0.10 second.

**Mecholyl Chloride (Acetylbetamethylcholine Hydrochloride).** On the same day that the effect of pressure on the carotid sinus was observed 15 mg of mecholyl chloride was administered subcutaneously. Before administration the blood pressure was 134 systolic and 82 diastolic. Two and one-half minutes after the drug was given,

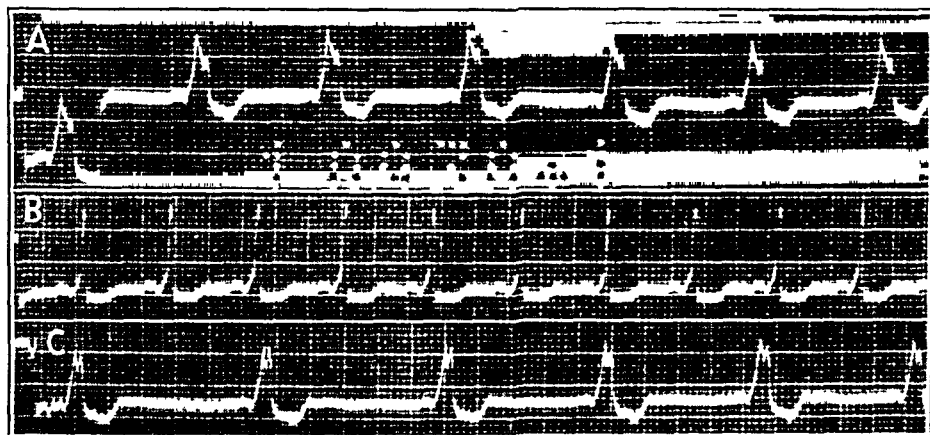


Fig 4—The effect of atropine sulfate on the widening of the QRS complex produced by digitalis (lead I). *A*, the tracing taken after digitalization, showing widening of the QRS complex. *B*, the tracing taken immediately after the intravenous injection of 12 mg of atropine sulfate. Note acceleration of the heart rate from 75 to 120 per minute and narrowing of the QRS complex from 0.14 to 0.07 second. *C*, the tracing taken twenty-four hours later, showing reappearance of the digitalis effect on the QRS time and a distinct arrhythmia.

the reading was 126 systolic and 76 diastolic and flushing, lacrimation, sweating and salivation appeared. A tracing was taken at this time and another one ten minutes later, when the blood pressure was 120 systolic and 76 diastolic. The only changes that took place in the electrocardiogram were an increase in heart rate from 95 to 120 per minute and more pronounced notching of the P wave in lead I. This change in the P wave was seen on other occasions when the rate increased (fig 3 *A* and fig 3 *B*). Eighteen minutes after mecholyl chloride was administered the heart rate was 110 per minute, the electrocardiogram was not altered in other respects.

Atropine sulfate, 12 mg, was then administered intravenously. The sweating, salivation, etc., immediately disappeared, and the blood pressure rose to 152 systolic and 92 diastolic. The electrocardiographic picture changed to a supra-

rate and a decrease in the QRS time to 0.07 second (fig 3 *A* and *B*). A tracing taken twenty-four hours later resembled the control record taken before the administration of atropine.

The effect of prostigmine methylsulfate following medication with atropine was studied on Aug 2, 1941. At this time the control tracing (fig 7 *B*) showed slight spontaneous widening of the QRS complex (heart rate 90 per minute). Atropine sulfate, 2 mg, given intravenously caused acceleration of the heart rate to 140 per minute and marked shortening of the QRS time (fig 7 *C*). Five minutes later prostigmine methylsulfate, 0.5 mg, was injected subcutaneously. Twenty minutes after the injection of prostigmine, the heart rate had slowed (110 per minute) and the QRS time had lengthened (fig 7 *D*). It is noteworthy that the QRS time after the administration of prostigmine slightly exceeded that in the control tracing taken before medication with atropine, in spite of the fact that the heart rate was faster.

In the experiments with atropine, mechoyl chloride and digitalis shortening of the QRS time was usually associated with acceleration of the heart rate and widening of the QRS time with a relatively slow rate. That the QRS time is not a function of heart rate is seen by a comparison of selected tracings shown

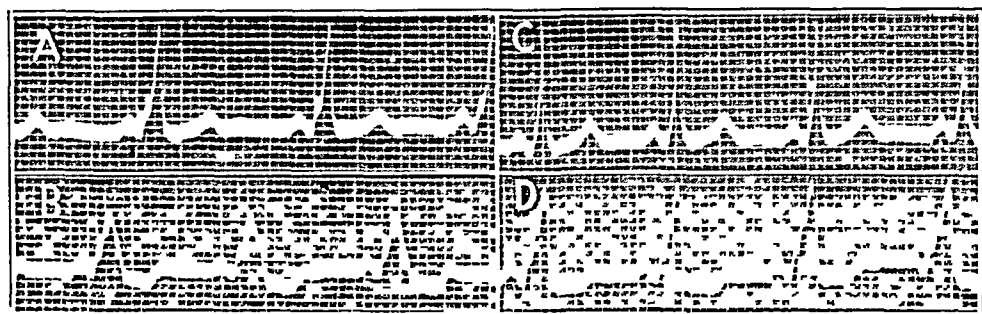


Fig 8—Lead II is shown. *A* and *B* compare two tracings in which the heart rate is different. The QRS time in the one with the faster rate (90 per minute) is 0.14 second (*B*), and the one with the slower rate (75 per minute) has a QRS time of 0.10 second (*A*). *C* and *D* show tracings in which the heart rates are essentially the same, the QRS time in one is 0.08 second (*C*) and in the other 0.12 second (*D*).

in figure 8. For instance, tracings with similar rates show widely different QRS durations, and a tracing with a slow rate may have a shorter QRS time than one with a faster rate. Thus, there is no correlation between the heart rate and the width of the QRS complex.

#### COMMENT

The condition in the case presented is classified as belonging to the syndrome of so-called "bundle branch block with short PR interval." However, it differs from that syndrome as heretofore described in the literature in that the QRS complex associated with the short PR interval was not consistently prolonged. Frequently, particularly in the early tracings, the QRS duration was only 0.09 second. It is possible that this case represents early stages in the evolution of the syndrome.

Opinions differ as to the pathogenesis and the significance of this electrocardiographic picture. The fact that in most instances the abnor-



and tracings were taken for four minutes (fig 6 C) There was no recurrence of the supraventricular type of nodal rhythm

The appearance of a nodal rhythm in 1 instance after medication with atropine after the administration of mecholyl chloride may be assumed to be due to the asynchronous release of the auriculoventricular node and the sinus node If the auriculoventricular node is partially released from the influence of the vagus nerve while the sinus node is still relatively under the control of this nerve, a nodal rhythm may appear spontaneously <sup>7</sup>

*Decreased Activity of the Vagus Nerve*—Exercise Acceleration of the heart rate by exercise had no effect on the electrocardiographic changes

*Atropine Sulfate* This compound, 12 mg, was given intravenously (May 6, 1940), and tracings (lead II) were taken immediately and two, four, six, eight and nine minutes later Resumption of the normal sinus rhythm did not occur No change in the PR interval was noted The QRS time decreased from 0.09 second

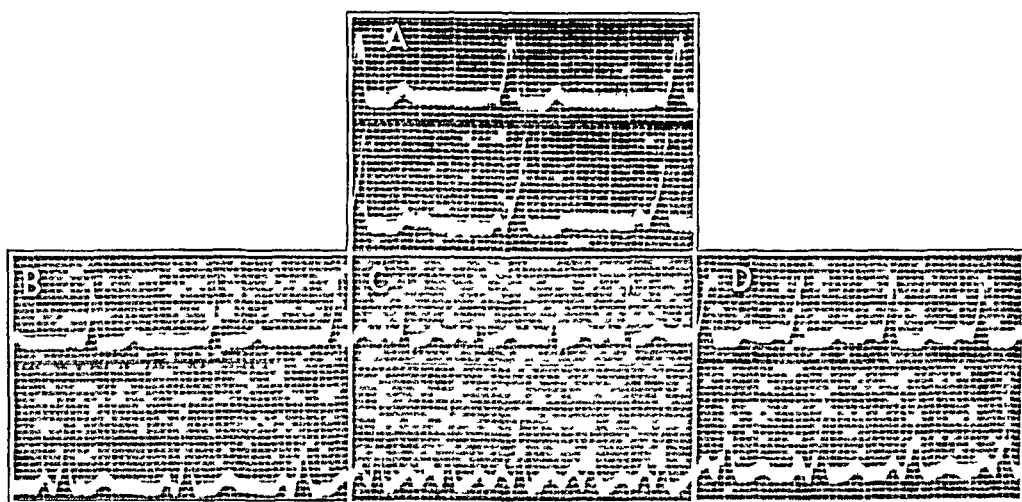


Fig 7—Leads I and II are shown A, the tracing taken July 7, 1941, showing spontaneous widening of the QRS complex (QRS time 0.11 to 0.12 second) The other three parts of the figure illustrate the effect of prostigmine methylsulfate on the QRS complex narrowed by atropine sulfate (Aug 2, 1941) B, the control record made before the administration of atropine sulfate C, the effect of atropine sulfate, 2 mg given intravenously Note the shortening of the QRS time from 0.09 to 0.05 second in lead I and from 0.10 to 0.08 second in lead II D, the effect of prostigmine methylsulfate, 0.5 mg, given subcutaneously five minutes after the atropine sulfate Note that the duration of the QRS complex is 0.10 second in lead I and 0.11 second in lead II and thus slightly exceeds that observed in the control record made before the administration of atropine sulfate

in the control record to 0.07 second after the administration of atropine The heart rate increased from 100 to 150 per minute

Subsequently (May 31), a larger dose, 2 mg, of atropine sulfate was administered intravenously Similar effects were noted, that is, acceleration of the heart

<sup>7</sup> Wilson, F N The Production of Atrioventricular Rhythm in Man After the Administration of Atropine, Arch Int Med 16 989 (Dec) 1915

the impulse in part passes by way of the "short cut" around the auriculo-ventricular node and in part travels by the normal pathway<sup>9a</sup> The hypothesis of aberrant auricular conduction has found experimental proof in the recent work of Butterworth,<sup>10</sup> who short circuited the normal conduction system of the auricle through an amplifier and produced a ventricular asynchronism with the electrocardiographic picture of so-called "bundle branch block with short PR interval" It is clear that under these conditions widening of the QRS complex is not synonymous with intraventricular block

In the case reported here the results of the experiments with digitalis are in favor of the last hypothesis Assuming that there are two pathways for the passage of impulses from the sinus node to the ventricles, one by way of the auriculoventricular node and one through the aberrant tissue, whatever depresses the function of the auriculoventricular node will tend further to short circuit auricular conduction, increase the asynchrony of the ventricular responses and lengthen the duration of the QRS complex The widening of the QRS complex by digitalis would thus result from the well known depressant action of the drug on the auriculoventricular node, causing the impulse from the sinus node to propagate to a greater extent through the aberrant tissue That this effect of digitalis on the QRS time is vagal is indicated by the fact that the widening is abolished by atropine

That our patient was susceptible to the influence of the vagus nerve is shown by the slowing of the heart rate and the appearance of an arrhythmia after the administration of digitalis, effects which may be attributable to an action on the sinus node A more striking demonstration of the role of vagal "tone" is the shortening of QRS time obtained by atropine in each of three experiments The atropine sulfate-prostigmine methylsulfate experiment also offers additional evidence that the widening of the QRS complex is in this case a function of the vagus nerve The fact that the widening of the QRS complex following administration of prostigmine slightly exceeded its duration in the control record taken before atropine was administered suggests that prostigmine may have contributed to the inhibition of cholinesterase

A similar effect of digitalis on the QRS complex associated with a short PR interval has been observed by Scherf and Schonbrunner<sup>11</sup> It is noteworthy, however, that in this instance the syndrome expressed itself in singly occurring beats rather than as an established rhythm or

10 Butterworth, J S The Experimental Production of the Syndrome of Apparent Bundle Branch Block with Short P-R Interval, *J Clin Investigation* **20** 458 (July) 1941

11 Scherf, D, and Schonbrunner, E Beitrage zum Problem der verkurzten Vorhofkammerleitung, *Ztschr f klin Med* **128** 750, 1935

mality is discovered in the early decades of life, in our case at the age of 20, has suggested that the cause may be a congenital defect of the conduction mechanism. Signs of organic cardiovascular disease are seldom evident in patients exhibiting this syndrome. In the case we have reported, however, the presence of arteriosclerosis and a tendency to hypertension make it impossible to rule out a structural change in the conduction system on an arteriosclerotic basis. In addition, in this case it is conceivable that the extensive tuberculosis may be a factor in the abnormal conduction. It is quite possible, on the other hand, that the arteriosclerotic and tuberculous processes are coincidental, rather than etiologic.

Since it is sometimes possible in this disorder to restore the electrocardiogram to normal by medication with atropine, it is generally believed that the syndrome represents a functional disturbance of conduction which is vagal in origin. In the first case reported,<sup>8</sup> the characteristic electrocardiographic abnormality appeared on stimulation of the vagus nerve and when spontaneously present could be abolished by administration of atropine.

The following theories have been advanced for the mechanism of this syndrome. First, the electrocardiographic abnormality represents nothing more than a nodal rhythm or tachycardia with aberrant conduction in the ventricle.

Here, the cause of aberrant conduction is probably similar to that seen in premature auricular systoles except that the aberrant by-pass remains fixed as long as the impulse arises in the A-V node.<sup>8</sup>

Second, it represents a regular sinus rhythm with functional intraventricular block.<sup>4</sup> Since the start of the QRS complex seems to be responsible for its lengthening and also for the shortening of the PR interval, according to this hypothesis the delay would occur in the upper part of the bundle, and the electrical effect of stimulation of the septum which is normally recorded as an isoelectric period, would become apparent.<sup>8</sup> Third, the syndrome represents a normal sinus rhythm with conduction by a direct pathway between the sinus node and the ventricle which results not in a block or delay but in an early arrival of the auricular impulse in the ventricular muscle.<sup>9</sup> This would imply that

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<sup>8</sup> Katz, L. N. *Electrocardiography*, Philadelphia, Lea & Febiger, 1941, p. 524.

<sup>9</sup> (a) Wolferth, C. C., and Wood, F. C. The Mechanism of Production of Short P-R Intervals and Prolonged QRS Complexes in Patients with Presumably Undamaged Hearts. Hypothesis of an Accessory Pathway of Auriculoventricular Conduction (Bundle of Kent), *Am Heart J* 8:297 (Feb.) 1933, (b) Further Observations on the Production of a Short P-R Interval in Association with Prolongation of the QRS Complex, *ibid* 22:450 (Oct.) 1941, (c) Kent, A. F. S. Some Problems in Cardiac Physiology, *Brit M J* 2:105 (July 18) 1914.

the amplitude and not to the duration of the QRS complex. Einthoven<sup>14</sup> in 1906 found that stimulation of the vagus nerve in dogs under chloroform anesthesia, which of itself increases vagal tone, did not produce any change in the form or the duration of the QRS complex. Ritchie<sup>15</sup> found that in human subjects likewise stimulation of the vagus nerve never resulted in a prolongation of QRS time, although in 1 instance a lengthening of the "ventricular beat" from 0.35 to 0.45 second was noted, this was at the expense, not of the QRS complex, but of the ST segment and the T wave. We have noted a similar lengthening of the QT interval by digitalis in this case.

The fact that in our case uniform effects were not obtained by the several methods employed to increase vagal activity does not necessarily argue against the correctness of the hypothesis as to the mechanism of the syndrome. For instance, differences in the cardiac response to faradic stimulation of the vagus nerve and to choline derivatives have been demonstrated.<sup>16</sup> It is possible that our patient did not have a sufficiently sensitive carotid sinus and that with respect to mecholyl chloride the dose may not have been large enough.

It is noteworthy that in the later tracings in this case progressive widening of the QRS complex occurred spontaneously and simulated the digitalis effect. This may have a bearing on the evolution of the syndrome and may be assumed to represent progressive depression of the auriculoventricular node with release of the aberrant conduction mechanism. The development of increased vagal tone is also seen in the slowing of the rate concomitant with the spontaneous increase in the QRS time. There was not, however, any constant relation between heart rate and the width of the QRS complex.

#### SUMMARY AND CONCLUSIONS

A case is reported in which the electrocardiographic picture of short PR interval in association with prolongation of the QRS complex was exhibited. Observations were made over a period of nearly two years.

The effect of changes in vagal activity produced in various ways was studied.

The effect of atropine sulfate on this syndrome was always to shorten the QRS time. This indicates that there was a vagal component in the mechanism of the syndrome.

14 Einthoven, W. Le télécardiogramme, *Arch. internat. de physiol.* **4**: 132, 1906.

15 Ritchie, W. T. The Action of the Vagus on the Human Heart, *Quart. J. Med.* **6**: 47 (Oct.) 1912.

16 Starr, I., Jr. A Note on the Antagonism Between the Cardiac Action of Acetyl- $\beta$ -Methylcholine and Acetyl Choline, and That of Quinidine, *J. Pharmacol. & Exper. Therap.* **56**: 77 (Jan.) 1936.

paroxysm Their observation that the abnormal beats disappeared after the administration of digitalis is contrary to the findings in our experiment and does not seem to us to justify their conclusion that digitalis has a greater affinity for the aberrant tissue than for the normal auriculo-ventricular conduction mechanism, since it is possible that the disappearance of the abnormal beats after digitalization may have been related to improvement in myocardial function

If one accepts either of the first two hypotheses, that the syndrome is essentially a nodal or a sinus rhythm with impairment of intraventricular conduction, one would be forced to conclude that the widening of the QRS complex by digitalis is due to an action on intraventricular conduction That digitalis ever possesses such an action has not been demonstrated satisfactorily The evidence of Hart,<sup>2</sup> frequently cited in favor of this action of digitalis, is open to question In the 2 cases presented by Hart the objections can be raised that there were present organic heart disease and congestive failure, which may of themselves give rise to transitory electrocardiographic changes including bundle branch block and that no data are submitted as to the dose of digitalis, the time of appearance or disappearance of the electrocardiographic change in relation to the medication or the reproduction of the change with repetition of digitalization Furthermore, the tracings illustrating the effect of digitalis on the QRS complex are not convincing, since in 1 case the widening of QRS time is insignificant (about 0.01 second) and in the other case the QRS configuration following medication with digitalis is so different from that in the control record that it is likely that the rhythm after administration of the drug originates in an ectopic focus (nodal?) This is not an unusual manifestation of the toxicity of digitalis and is due to an action on the pacemaker rather than on intraventricular conduction Winternitz<sup>12</sup> studied the effect of digitalis on the QRS complex in patients in cardiac failure and observed changes in its amplitude but no prolongation This is in agreement with general clinical experience

Not only is there inadequate evidence to establish the existence of a digitalis effect on intraventricular conduction, but there is a lack of satisfactory proof that stimulation of the vagus nerve by other means than medication with digitalis can influence intraventricular conduction Changes in the ventricular complex during the stimulation of the vagus nerve in dogs were recorded by Hering in 1909,<sup>13</sup> but these applied to

12 Winternitz, M Die Digitaliswirkung auf das menschliche Kammelektrogramm, *Ztschr f Kreislaufforsch* **23** 452, 1931

13 Hering, H E Experimentelle Studien am Säugetieren über das Elektrokardiogramm, *Arch f d ges Physiol* **127** 155, 1909

# STORAGE AND SIGNIFICANCE OF TISSUE GLYCOGEN IN HEALTH AND IN DISEASE

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The glycogen in animal tissues has engaged the attention of physiologists since the early work of Claude Bernard. Its significance in health and in disease has also been the subject of scattered observations by clinical investigators since that time. This presentation is an attempt to summarize and correlate such physiologic and clinical aspects of the subject as may be of interest and importance to the practicing physician.

## NATURAL OF GLYCOGEN

Glycogen is a condensation product, or polymer of dextrose (*d*-glucose). A molecule of glycogen is composed of twelve units of dextrose, some water being withdrawn in the process of condensation<sup>1</sup>. This product is not peculiar to animal tissue. Starch is similar in its structure and chemistry. However, within the living cell glycogen exists in a characteristic state, which is different from that of glycogen in the chemist's bottle or of starch on the grocer's shelf. In its natural habitat glycogen exists in the colloidal state, the particles of glycogen being composed of large aggregates of glycogen molecules. It seems likely that the colloidal state of the glycogen is preserved by the protective action of certain proteins within the cell<sup>2</sup>.

The physical structure of glycogen may explain the manner in which it is protected from the metabolic activities of the cell which are going on all around it. Carbohydrate is being synthesized and broken down constantly. Under these circumstances the accumulation of more than a small equilibrium amount of glycogen would be difficult to explain from a chemical standpoint were it not for the physical protective barrier of the colloidal state which withholds it from the reaction mixture. This is a phenomenon well known to enzyme chemists. Conversely, the dis-

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<sup>1</sup> Haworth, J. Constitution of the Sugars, London, Edward Arnold & Co 1929.

<sup>2</sup> Lazarow, A. Particulate Glycogen, Science 95:49, 1942.

In repeated experiments digitalis uniformly produced widening of the abnormal QRS complex. That this effect involves vagal function was demonstrated by its disappearance after administration of atropine.

The results of this study are in harmony with the hypothesis that this syndrome is due to an aberrant conduction mechanism joining the sinoatrial node with one of the ventricles. According to this hypothesis the widening of the QRS complex by digitalis is due not to an action of the drug on intraventricular conduction, but rather to depression of the auriculoventricular node, resulting in increased activity of the aberrant auricular conduction tissue with consequent increased asynchrony of the ventricular responses.

NOTE Since this paper was submitted for publication, Butterworth's experiments have been reported in greater detail.<sup>17</sup>

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<sup>17</sup> Butterworth, J. S., and Poindester, C. A. Short PR Interval Associated with a Prolonged QRS Complex, *Arch Int Med* **69** 437 (March) 1942.

groups is the primary means by which the cell derives useful energy from the breakdown of foodstuffs<sup>4</sup>

In the living animal the transformation of dextrose to glycogen is facilitated by the presence of insulin. The increased deposition of glycogen from dextrose under the influence of insulin, particularly in muscle, is the most firmly established physiologic action of this hormone. However, insulin is not essential to the reaction, since it has been shown that small amounts of glycogen may be deposited in the absence of insulin by the diabetic organism.<sup>5</sup> This fact has received final confirmation from the *in vitro* work of Coll and co-workers,<sup>3</sup> who have synthesized glyco-

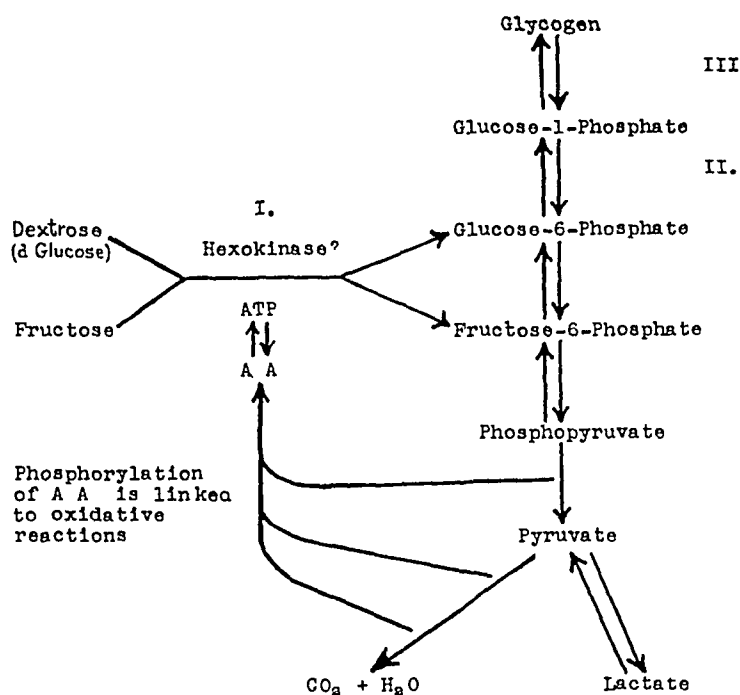


Fig 2—The probable manner in which the transformation of dextrose to glycogen is facilitated by insulin. The hormone probably acts at an intermediate step between the hexose phosphates and pyruvic acid and by facilitating certain phosphorylations in this region makes possible the continuous rephosphorylation of adenylate (*AA*) to adenosine triphosphate (*ATP*) and thus indirectly increases the rate of phosphorylation of *d*-glucose (dextrose) to glucose-6-phosphate.

gen from dextrose in the test tube in the presence of the necessary enzymes but without insulin. Indeed, they were unable to demonstrate any effect when insulin was added to their system. From this and other evidence it seems unlikely that insulin acts on any of the series of reac-

4 Kalckar, H. Nature of Energetic Coupling in Biological Syntheses, *Chem Rev* **28** 71, 1941.

5 Major, S. G., and Mann, F. C. The Formation of Glycogen Following Pancreatectomy, *Am J Physiol* **102** 409, 1932.





insulin did not exert any significant effect in addition to the effect of sugar concentration. It may be stated parenthetically that this relation of the action of insulin to sugar concentration is consistent with other actions which we have been able to demonstrate.<sup>6a</sup> In other words, insulin enables the tissues to do at low or at physiologic concentrations of sugar that for which they would otherwise require high concentrations.

#### BREAKDOWN OF GLYCOGEN

Since glycogen is the intracellular storage form of carbohydrate, it is the most readily available source of energy for the body. When glyco-

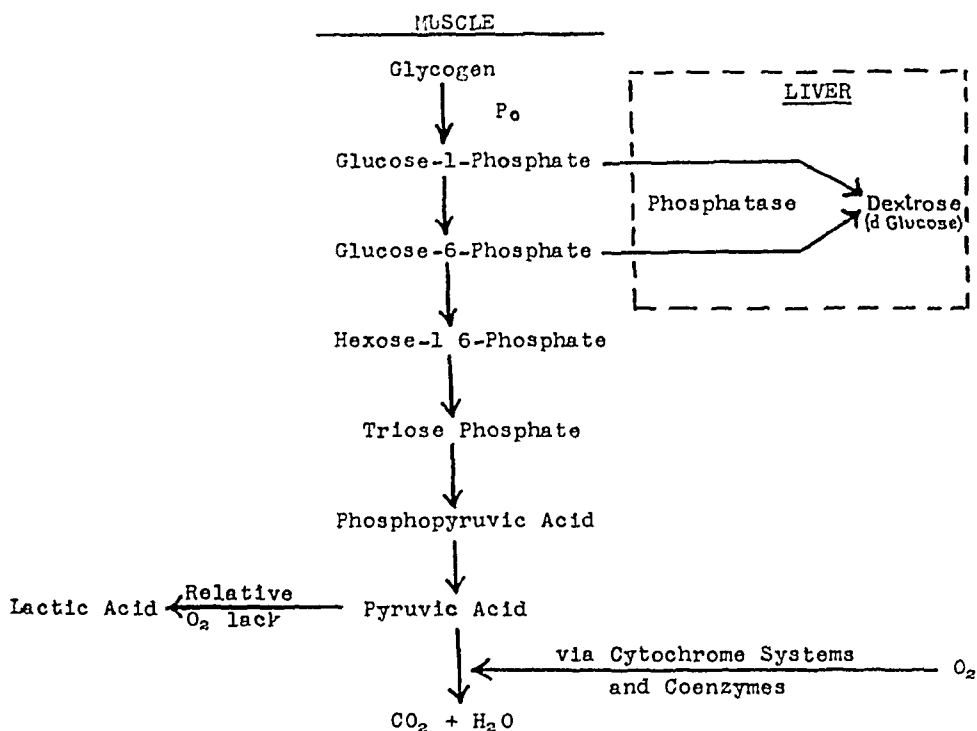


Fig. 4—The chemical steps involved in the breakdown of glycogen in the muscle and in the liver under ordinary physiologic conditions

gen breaks down in the muscle under ordinary physiologic conditions, all of it goes through a series of intermediary steps ending in carbon dioxide and water (fig. 4). Lactic acid does not appear under these conditions, and it will be noted from figure 4 that lactic acid is to be regarded as an offshoot from the series of reactions, rather than a direct step in them. The steps from glycogen to pyruvic acid can occur in the absence of oxygen. The steps below pyruvic acid depend on an adequate oxygen supply. When because of an excessively rapid rate of breakdown of glycogen or some impairment in oxygen supply the later steps can no longer keep pace with the early steps, pyruvic acid tends to accumulate. But under these same conditions pyruvic acid is rapidly converted to and appears as lactic acid. Once the disproportion between the rates

tions indicated in figure 1. The work of my associates and myself<sup>6</sup> makes it probable that insulin acts at an intermediate step between the hexose phosphates and pyruvic acid, as shown in figure 2. By facilitating certain phosphorylations in this region it makes possible the continuous rephosphorylation of adenylic acid (*AA*) to adenosinetriphosphate (*ATP*) and thus indirectly increases the rate of phosphorylation of *d*-glucose (dextrose) to glucose-6-phosphate.

The major factor other than insulin which determines the rate of synthesis of glycogen is the concentration of sugar present. This is, of course, in accord with the general nature of all enzyme reactions. Cori and Cori<sup>7</sup> have shown that the amount of glycogen deposited in the liver of a given experimental animal depends on the height at which the blood sugar level is maintained, rather than on the total amount of sugar

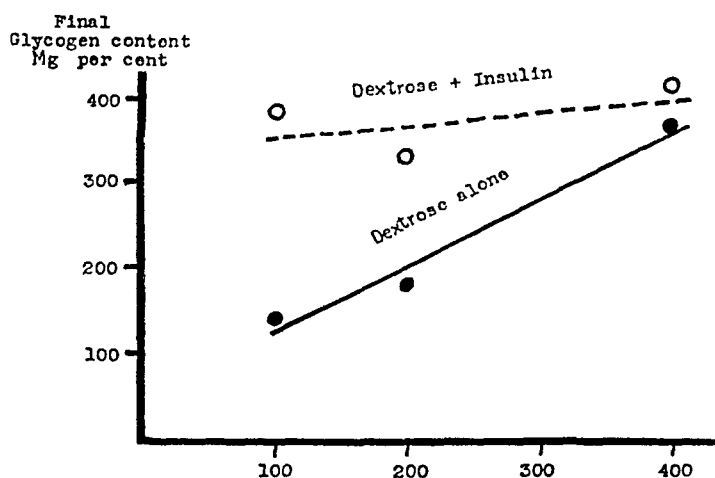


Fig. 3—The increasing amounts of glycogen deposited in muscle in vitro at increasing concentrations of blood sugar, with and without added insulin

given. It has been possible in our own laboratory<sup>8</sup> to demonstrate this relation for muscle even more clearly on rat diaphragm in vitro by the Warburg technique. Figure 3 shows the increasing amounts of glycogen deposited at increasing sugar concentrations, with or without added insulin. It will be noted that at the highest concentrations of sugar the

6 (a) Soskin, S., and Levine, R. On the Mode of Action of Insulin, *Am J Physiol* **129** 782, 1940. (b) Levine, R., Feinstein, R. N., and Soskin, S. Studies on the Mechanism of Insulin Action in Skeletal Muscle in Vitro, *Federation Proc* **1** 50, 1942.

7 Cori, C. F., and Cori, G. T. The Influence of Insulin and Epinephrine on Glycogen Formation in the Liver, *J Biol Chem* **85** 275, 1929.

8 Hechter, O., Levine, R., and Soskin, S. Relationship Between Sugar Concentration and Glycogenetic Action of Insulin on Rat Diaphragm in Vitro. *Proc Soc Exper Biol & Med* **46** 390, 1941.

in glycogenesis. There is no known influence of insulin on the activity of amylase. Hence the intervention of amylase in toxemic states introduces a factor in breakdown of glycogen which cannot be controlled by insulin, regardless of the amounts of insulin administered.

#### SIGNIFICANCE OF MUSCLE GLYCOGEN

The glycogen within the muscle cells may be reasonably supposed to serve best in emergencies, when the muscle is unable to draw sugar from the blood as quickly as it requires it. But, as a matter of fact, glycogen is more than merely a conveniently packaged form of carbohydrate lying on the pantry shelf. It is now known that more energy is derivable from a certain amount of glycogen than from an equivalent

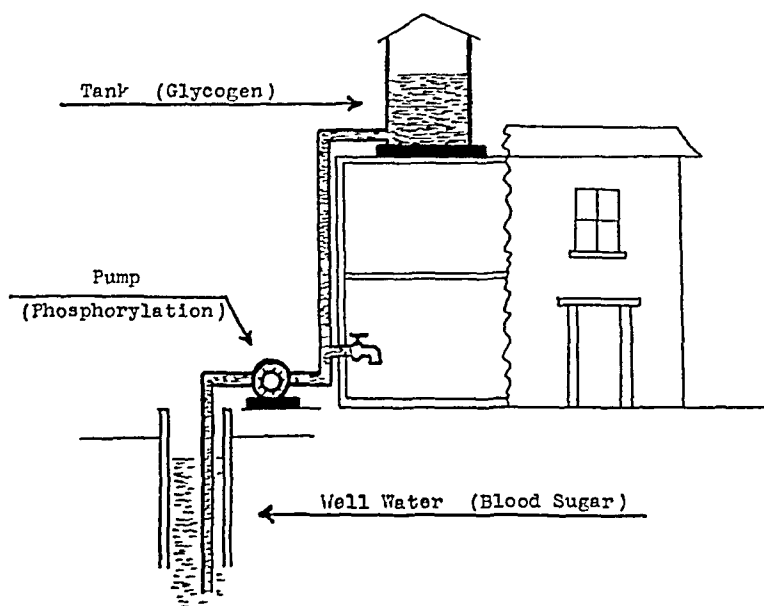


Fig 5—A graphic representation of the significance of muscle glycogen, in which the water in the well represents the blood sugar, the pump represents the phosphorylating mechanisms and the tank on the roof represents the store of glycogen.

amount of blood sugar. It requires a certain amount of energy to bring the blood sugar into the metabolic system of the muscle (as hexose-6-phosphate), and therefore all the energy inherent in the dextrose is not available for useful work. On the other hand, the breakdown of glycogen to the same stage does not require the addition of energy and hence makes all its inherent energy quickly available. This is not to say that one gets something for nothing from glycogen, for it required some energy to build up the glycogen in the first place. But this energy was expended during a quiescent period when plenty of it was available. The situation is analogous to that portrayed in figure 5. Here, the water in the well represents the blood sugar, the pump stands for the phosphory-

at which glycogen is broken down and oxygen is supplied has disappeared, the lactic acid may gradually be oxidized back to pyruvic acid and further to carbon dioxide and water. Meanwhile, however, much of the lactic acid may have diffused out into the blood stream. This lactic acid which appears in the blood under conditions of violent exercise or of relative anoxia is carried to the liver and there reconverted to glycogen. The so-called "lactic acid cycle" is of some significance for the conservation of carbohydrate under conditions of stress and strain but is of no particular importance normally when lactic acid does not pile up in muscle.

Practically all the tissues in the body which have been studied exhibit a pattern of breakdown of glycogen similar to that described for muscle. The liver differs in one respect. This difference does not concern the steps in the direct series of reactions down to carbon dioxide and water but is due to an additional factor which results in the appearance of dextrose as one of the chief end products of breakdown of glycogen. The additional factor is the presence of an active phosphatase which, by splitting the phosphate from hexose phosphates, can divert a large proportion of these intermediate substances from the direct line of degradation.<sup>9</sup>

It will be noted that there is no place in figure 4 for the participation of amylase or glycogenase in the breakdown of glycogen. Such an enzyme was at one time supposed to be responsible for normal glycogenolysis. It now appears that the amylase present in blood is merely an incidental constituent which has diffused out from the parotid and the pancreatic glands. When the liver has been washed free of blood under proper conditions, it is not possible to demonstrate any amylase activity in hepatic tissue. This may be either because the membrane of the hepatic cells excludes the blood amylase or because of the demonstrated fact that there is insufficient chloride ion ( $\text{Cl}^-$ ) within the hepatic cell to allow for amylase activity even if the enzyme could enter. However, under abnormal conditions amylase may assume an important role in breakdown of glycogen. It has recently been demonstrated in our laboratory<sup>10</sup> that the livers removed from animals intoxicated with diphtheria toxin exhibited significant amylase activity within the liver cells. This may explain in part the low levels of liver glycogen in infection and in toxemia, as well as the occurrence of so-called "insulin resistance" under the same conditions. As previously mentioned, insulin probably exerts its influence on the phosphorylating mechanisms involved

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9 Cori, C. F. Glycogen Breakdown and Synthesis in Animal Tissues, *Endocrinology* **26** 285, 1940

10 Taubenhaus, M., and Soskin, S. On the Mechanism of Insulin Resistance in Toxemic States, *J. Clin. Endocrinol.* **2** 171, 1942

## SIGNIFICANCE OF LIVER GLYCOGEN

The prime function of the liver in respect to carbohydrate metabolism is to supply sugar to the blood and through this medium to all the other tissues of the body<sup>15</sup> The rate at which it secretes sugar into the blood is governed by a remarkably efficient homeostatic regulating mechanism which is responsible for the so-called "normal blood sugar level"<sup>16</sup> When sugar is not available from the gastrointestinal tract for any considerable length of time, it must be made by the liver from noncarbohydrate materials The liver glycogen thus represents a reserve of carbohydrate on which the liver may draw quickly while the gluconeogenic processes are accelerating to an adequate rate While this reserve is important for temporary emergencies, it is not always sufficiently appreciated that it represents a rather small amount of carbohydrate, as compared to the body's daily requirements If one assumes, for example, that a man weighing 70 Kg with a liver weighing 1,800 Gm has an average good store of glycogen of about 6 per cent, this would mean a total liver glycogen of 108 Gm If gluconeogenesis were to cease, this amount of carbohydrate could supply the requirements of his extrahepatic tissues (roughly 0.25 Gm per kilogram per hour) for about six hours only The relative importance of the gluconeogenic processes as compared to the reserve of liver glycogen is obvious

In view of the foregoing statements it is not surprising that recent work has shown that the anterior lobe of the pituitary gland, the adrenal cortex and the thyroid, as well as the pancreas, exert their important effects on carbohydrate metabolism through the gluconeogenic processes in the liver<sup>17</sup> It is beyond the scope of this presentation to go into detail as to the particular effects of these glands It is important to note, however, that while the anterior lobe of the pituitary, the adrenal cortex and the thyroid all increase the rate of gluconeogenesis in the liver, the activity of none of them results in increased stores of glycogen when there is a relative or an absolute insulin deficiency It is equally important to remember that the normal animal or human being secretes an optimal amount of insulin for storage of glycogen in the liver The administration of additional insulin to the normal organism, by causing

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15 Soskin, S The Liver and Carbohydrate Metabolism, *Endocrinology* **26** 297, 1940, The Blood Sugar Its Origin, Regulation and Utilization, *Physiol Rev* **21** 140, 1941

16 Soskin, S, Essex, H E, Herrick, J F, and Mann, F C The Mechanism of Regulation of the Blood Sugar by the Liver, *Am J Physiol* **124** 558, 1938

17 Soskin, S Metabolic Functions of the Endocrine Glands, *Ann Rev Physiol* **3** 543, 1941

lating mechanisms and the tank on the roof represents the store of glycogen. It is readily understandable that when the tank contains stored water, the tap can deliver a rate of flow far beyond the rate-capacity of the pump. The water stored during periods when the tap is closed is at a higher level than the original source of the water and also stores some of the energy applied by the pump. This potential energy is released when the tap is opened. Too great an outflow from the tap may, of course, exhaust the stored water and reduce the flow from the tap to the rate at which the pump is capable of operating. A similar situation may occur in muscle, when excessive rates of work over prolonged periods are attempted.

The application of these physiologic facts to clinical phenomena is exemplified by the greater stores of glycogen and of phosphate esters found in the muscles of animals trained to perform prolonged work<sup>11</sup>. This may be related to the physical abilities of manual laborers and of athletes. Conversely, the characteristically low levels of muscle glycogen found in persons with poorly controlled diabetes and in hyperthyroid persons is accompanied by muscular weakness.

The skeletal muscle, to which the foregoing remarks apply, is an organ which must of necessity undertake bursts of exertion. The role of glycogen does not seem to be as important in other organs which characteristically work at more constant rates. For example, the glycogen content of the central nervous system seems to have little significance, for this tissue apparently derives its energy from the blood sugar from moment to moment<sup>12</sup>. Hence its extreme sensitivity to hypoglycemia. The cardiac muscle may be said to occupy a position in between the extremes represented by the central nervous system, on the one hand, and skeletal muscle, on the other. While the heart must vary its output of energy considerably, it does not do so throughout a range comparable to that of skeletal muscle. Its glycogen stores are correspondingly less important. The work of Cruickshank and Kosterlitz<sup>13</sup> has shown that it uses blood dextrose preferentially to glycogen and the latter preferentially to lactic acid. However, its stores of glycogen undoubtedly serve it during hypoglycemia, for the heart is not particularly sensitive to this condition. The damaged heart with poor stores of glycogen is more vulnerable. In this condition stenocardial symptoms may be precipitated by a rapid fall of the blood sugar<sup>14</sup>.

11 Palladin, A. The Biochemistry of Muscle, *Bull. Soc. chim. biol.* **13** 13, 1931.

12 Quastel, J. H. Respiration in the Central Nervous System, *Physiol. Rev.* **19** 135, 1939.

13 Cruickshank, E. W. H., and Kosterlitz, H. W. The Utilization of Fat by the Aglycaemic Mammalian Heart, *J. Physiol.* **99** 208, 1941.

14 Soskin, S., Katz, L. N., Strouse, S., and Rubinfeld, S. H. Treatment of Elderly Diabetic Patients with Cardiovascular Disease. Available Carbohydrate and Blood Sugar Level, *Arch. Int. Med.* **51** 122 (Jan.) 1933.

hyperglycemia and glycosuria have been controlled. But this is not necessarily so, unless the means by which the control was accomplished has also led to increased stores of glycogen in the body tissues. From this point of view the use of a substance like decamethylenediguanidine (synthalin), which depresses gluconeogenesis by damaging the liver, is obviously wrong and dangerous regardless of how well it may control the more obvious criteria of diabetes. The high fat diet may be considered to be in the same category, although not nearly so dangerous.

When carbohydrate administration to supplement insulin therapy is advocated for the treatment of diabetic coma, it is often objected that the comatose person is already saturated with sugar, so that the administration of more carbohydrate is useless. A little simple arithmetic will show that this concept is erroneous. The stores of glycogen of such a

*Carbohydrate Required to Restore a Comatose Diabetic Person to Normal by the End of the First Twenty-Four Hours of Treatment with Insulin*

Subject A man weighing 70 Kg, with a liver weighing 1,800 Gm, muscle weighing 35 Kg and 21 liters of blood and extracellular fluid

	Diabetic Gm	Normal Gm
Liver glycogen	9 (0.5 %)	108 (6.0 %)
Muscle glycogen	70 (0.2 %)	245 (0.7 %)
Extracellular sugar	74 (0.35 %)	17 (0.08 %)
	<hr/> 153	<hr/> 370
		153
Carbohydrate requirement for replenishment of stores, Gm		217
Carbohydrate requirement for 24 hour utilization, Gm (based on 50% of 2,100 calories)		263
Total, Gm		<hr/> 480

person are negligible. The available carbohydrate is chiefly that which is present in the blood. The accompanying calculation clearly shows the inadequacy of his extracellular sugar, as compared to the amount necessary to replenish his stores of glycogen and supply his caloric requirements, as the carbohydrate metabolism reverts to normal under the influence of insulin.

It is evident that almost 500 Gm of carbohydrate must be administered to this hypothetical person during the first twenty-four hours of treatment and about one half of that amount during subsequent days in order to maintain normal stores of glycogen and carbohydrate metabolism.

The storage and significance of glycogen in health and in disease, while dramatically illustrated in diabetic patients, is sufficiently important in patients suffering from other conditions and in normal persons to merit careful attention at all times.



a rapid withdrawal of blood sugar into the much bulkier peripheral tissues, results in a greater demand on the liver and an actual lowering of the liver glycogen<sup>18</sup>

I have previously noted the generally observed association of good stores of glycogen with healthy liver tissue and have suggested that the normal protein structure of the liver cell is essential for glycogen storage. There is considerable evidence that the converse is also true, namely, that good stores of glycogen in the liver cell protect its protein structure. It is possible that the fundamental mechanism may be similar in both instances, that is the preservation of the normal colloidal state. This is merely a speculation, but the fact that glycogen is protective seems certain on an empiric basis<sup>19</sup>. There is ample evidence that hepatic damage due to various injurious agents is minimized in the presence of adequate stores of glycogen. The practical therapeutic application of this knowledge through the use of high carbohydrate treatment is well known<sup>20</sup>. Aside from the possible direct protective action to the hepatic cell, good stores of glycogen may also be necessary for detoxification of the noxious agents coming to the liver. These reactions have recently been studied *in vitro*. It is known that many such agents are rendered harmless by conjugation with glucuronic acid or by acetylation both of which processes require the use of carbohydrate by the liver<sup>21</sup>. A lack of available carbohydrate may allow the toxic agents to damage the liver unduly before they are neutralized.

#### CERTAIN PRACTICAL CONSIDERATIONS

It has been shown that glycogen not only is a storage product which supplies sudden demands for carbohydrate by the body but is a substance which is important for the well-being and the functional integrity of the tissues. These considerations are particularly important in the treatment of diabetes, in which the lack or the relative lack of insulin interferes with storage of glycogen. It has been an all too common fallacy to assume that a diabetic person has been restored to the normal state because

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18 Bridge, E. M. The Action of Insulin on Glycogen Reserves, *Bull. Johns Hopkins Hosp.* **62** 408, 1938.

19 (a) Soskin, S., and Hyman, M. Physiologic Basis of Intravenous Dextrose Therapy for Diseases of the Liver, *Arch. Int. Med.* **64** 1265 (Dec.) 1939. (b) Holmes, E. The Effect of Toxaemia on Metabolism, *Physiol. Rev.* **19** 439, 1939.

20 Strouse, C. D., Rosenbaum, E. E., Levy, R. E., and Soskin, S. Intensive Carbohydrate Therapy in Diabetic Patients with Manifest or Suspected Liver Disease, *J. Clin. Endocrinol.* **1** 831, 1941. Soskin and Hyman<sup>19a</sup>.

21 Lipschitz, W. L., and Bueding, E. Mechanism of the Biological Formation of Conjugated Glucuronic Acids, *J. Biol. Chem.* **129** 333, 1939. Klein, J. R., and Harris, J. S. The Acetylation of Sulfanilamide *in Vitro*, *ibid.* **124** 613, 1938.

lacks. With the demonstration of anti-Rh antibodies in the serum of a large percentage of the mothers of erythroblastotic infants the plausible hypothesis was advanced that erythroblastosis foetalis is the result of an intrauterine antigen-antibody reaction<sup>4</sup>. Further work has shown that an additional 7 per cent of erythroblastotic infants have mothers whose blood contains Rh antigen but who lack a genetically related antigen designated hR, which the babies have. It seems likely that eventually all cases of erythroblastosis may be shown to depend on these or similar factors.

In the light of the foregoing facts this study was undertaken to determine to what extent the blood picture in erythroblastosis foetalis simulates the picture seen in experimental anemias due to autoantibodies.

#### METHOD AND MATERIAL

Records and blood smears in 24 cases of fetal hydrops and of icterus gravis neonatorum were studied. In 7 cases these were personally obtained, and in the remainder they were obtained through Dr Carl T. Javert, of the Department of Obstetrics, and Dr Carl Smith, of the Department of Pediatrics.

The smears obtained from the obstetric service were all of cord blood drawn at birth from the umbilical vein, the others were of peripheral blood obtained by finger prick or heel prick. All smears were stained by the usual Romanowsky technic. Hemoglobin determinations were made by the Sahli-Hellige method. Red cell counts were made with red cell pipets standardized by the United States Bureau of Standards. Reticulocytes were stained *in vivo* with 0.5 per cent brilliant cresyl blue and the number of reticulocytes per five hundred red cells counted in dried smears counterstained with Romanowsky stains (Hastings' stain or Wright's stain).

Price-Jones curves were made by the direct measurement of the diameters of three hundred consecutive round cells in dried smears with an ocular micrometer scale calibrated to measure to 0.7 micron. Fields were selected where the cells were not in contact with each other, where they were uniformly distributed and where there was a minimum of distortion of their outlines. At the outset of the study several curves were done by different observers as a check. In the cases which came under personal observation curves were made at frequent intervals until the blood picture had returned to normal. In several instances when the figures obtained from counting three hundred cells seemed open to question an additional three hundred cells were counted and the total figures divided by 2.

For controls, smears of cord blood taken at birth and peripheral blood taken four hours after birth were made on 5 normal newborn infants of mature weight (more than 2,500 Gm.) and the diameters of three hundred consecutive round cells per smear counted. The combined results for the three thousand cells were reduced to a scale of three hundred cells for comparison. Red cell counts and hemoglobin determinations were also made. In addition, Price-Jones curves were

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<sup>4</sup> This hypothesis had been previously advanced by Darrow (Icterus Gravis [Erythroblastosis] Neonatorum. Examination of Etiologic Considerations, Arch. Path. 25:378 [March] 1938) on the basis of the clinical and pathologic evidence but with no knowledge of the specific antibodies involved.

# MORPHOLOGY OF ERYTHROCYTES IN ERYTHROBLASTOSIS FOETALIS

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MEDICAL CORPS, ARMY OF THE UNITED STATES

Acute hemolytic anemias due to autoantibody reactions have been observed in human beings<sup>1</sup> and induced experimentally in animals<sup>2</sup> Hematologic examination of the experimental animals has revealed a fairly consistent pattern of morphologic change During the initial phase of hemolysis, the mean cell diameter decreases and the mean cell volume increases, the cells assuming a spheroid shape After several days the mean diameter rises above normal with the simultaneous appearance of macrocytes, nucleated red cells and increased numbers of reticulocytes At this time the Price-Jones curve is frequently bimodal, and Dameshek has stressed this point as being of diagnostic import in such anemias

The recent work of Levine and his associates<sup>3</sup> has shown that about 90 per cent of infants with erythroblastosis foetalis have an antigen, designated as Rh, in their blood cells which is inherited from the father, probably as a mendelian dominant character, and which the mother

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From the New York Hospital and the Department of Pediatrics, Cornell University Medical College

1 (a) Dameshek, W, and Schwartz, S O Acute Hemolytic Anemia (Acquired Hemolytic Icterus, Acute Type), *Medicine* **19** 231, 1940, (b) The Presence of Hemolysins in Acute Hemolytic Anemia Preliminary Note, *New England J Med* **218** 75, 1938 (c) Farrar, G E, Burnett, W E, and Steigman, A J Hemolysinemia and Hepatic Degeneration Cured by Splenectomy, *Am J M Sc* **200** 164, 1940 (d) Reisner, E H, Jr, and Kalkstem, M Auto-hemolysinemia with Auto-Agglutination Report of a Case with Splenectomy, *ibid* **203** 313, 1942

2 (a) Price-Jones, C The Variation in the Sizes of Red Blood Cells, *Brit M J* **2** 418, 1910 (b) Passey, R D, and Braine, J F C Variations in the Size of the Red Cells in Some Experimental Anaemias in Rabbits, *Guy's Hosp Rep* **74** 217, 1924 (c) Filo, E Anemies hemolytiques provoques par le serum erythrolytique, *Sang* **10** 178, 1936 (d) Dameshek, W, and Schwartz, S O Hemolysins as the Cause of Clinical and Experimental Hemolytic Anemias, *Am J M Sc* **196** 769, 1938 (e) Tigertt, W D, and Duncan, C N Erythrocyte Morphology in Experimental Hemolytic Anemia as Induced by Specific Hemolysin, *ibid* **200** 173, 1940 (f) Whipple, A O Observations on the Function of the Spleen with Reference to the Familial Hemolytic Anemias, paper read at the meeting of the New York Academy of Medicine, Section of Surgery, Feb 6, 1942

3 Levine, P, Burnham, L, Katzin, E M, and Vogel, P The Role of Iso-Immunization in the Pathogenesis of Erythroblastosis Fetalis, *Am J Obst & Gynec* **42** 925, 1941

was severe, and the infants either were stillborn or died shortly after birth. The curves of the remaining 6 infants showed peaks at 70 and 84 microns (fig 1)

There were 11 cases of icterus gravis, in 3 cases the infants were stillborn, in 1 death occurred at four days and in 7 the infants recovered. One unclassified baby died the day after birth. Of these 12 patients, 10 showed a bimodal curve at 70 and 84 microns on the initial examination of the blood, and for 1 such a curve developed on the third day of

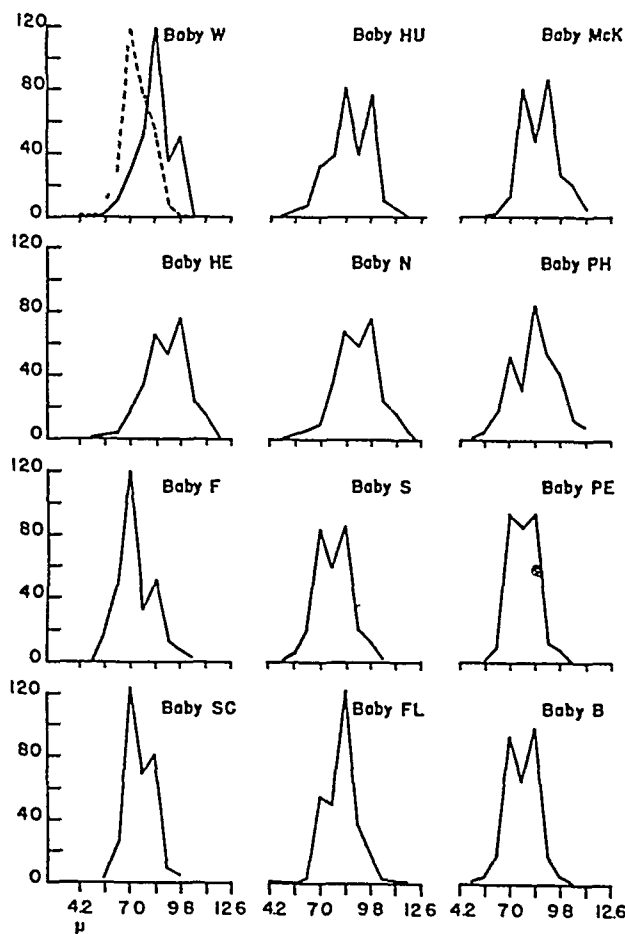


Fig 1—Price-Jones curves (three hundred cells each) made on 12 infants with fetal hydrops. (The dash line is a control curve.)

life (case 5, baby I). The curve for 1 (case 1, baby D) was monophasic with a microcytic peak at 56 microns. This patient did not come under personal observation, so it was unknown whether a bimodal curve developed later, but a smear of blood taken after recovery was essentially normal (table 2 and fig 2).

In the 5 infants observed until recovery a definite pattern can be demonstrated (figs 3 through 7). Both baby B (case 3, fig 3) and

made for 12 infants between the ages of 2 hours and 1 month suffering from prematurity and diarrhea (2), intracranial hemorrhage (2), asphyxia neonatorum (2), pyloric stenosis (1), pylorospasm (1), infection (3) and obstructive jaundice (1). Several of these infants (fig 9) had marked anemia. In 2 instances Price-Jones curves for three hundred consecutive reticulocytes were made.<sup>5</sup>

In 600 cases of marked erythroblastemia differential counts were made on one hundred consecutive nucleated red cells. The cells were identified according to the classification advocated by Dameshek and Valentine<sup>5</sup> and Jones,<sup>6</sup> slightly modified as follows:

**Proerythroblast** This type of cell is large, with deeply basophilic cytoplasm containing one or more vacuoles and a lighter nucleus filling most of the cell, in which the chromatin is arranged in a uniform, scroll-like pattern, with several nucleoli.

**Megaloblast A** Only slightly smaller than the preceding cell, this type has a basophilic cytoplasm and a nucleus in which the chromatin is still scroll-like in character.

**Megaloblast B** In this cell the cytoplasm is polychromatic and the nucleus is smaller. The nuclear chromatin is clumped in coarse strands like a ball of yarn but is still less clumped than that in the corresponding cell of the normoblast series.

**Normoblast A** The cytoplasm resembles that of megaloblast A, but the cell is slightly smaller, and the nuclear chromatin shows definite clumping.

**Normoblast B** The cytoplasm is polychromatic, and the nucleus shows a definite pattern of clumping, often resembling the spokes of a wheel (*Radkern*) or a clock face.

**Orthochromatic mixed group** Since in the final stages of maturation it is often impossible to differentiate normoblasts and megaloblasts from each other, all orthochromatic nucleated red cells with pyknotic nuclei were arbitrarily placed in this group.

For the sake of consistency all patients who exhibited even a small amount of edema were classified as having fetal hydrops and the remainder as having icterus gravis, except for 1 infant (baby TH), who exhibited neither edema nor icterus and is listed as unclassified.

## RESULTS

There were 12 cases of fetal hydrops, in 5 cases the infants were stillborn, in 4 they died shortly after birth and in 3 they recovered. In all cases the Price-Jones curve was bimodal at the time of the first examination of the blood. In 6 instances the peaks were at 8.4 and 9.8 microns. As can be seen from table 1, in all these cases the condition

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<sup>5</sup> Dameshek, W., and Valentine, E. The Sternal Marrow in Pernicious Anemia. Correlation of Observations at Biopsy with Blood Picture and Effects of Specific Treatment in Megaloblastic ("Liver-Deficient") Hyperplasia, *Arch Path* **23** 159 (Feb) 1937.

<sup>6</sup> Jones, O. P. Cytology of Pathologic Marrow Cells with Special Reference to Bone Marrow Biopsies, in Downey, H. Handbook of Hematology, New York, Paul B. Hoeber, Inc., 1938, vol. 3, p. 2045.

baby FL (case 4, fig 4) showed a definite preponderance of macrocytes at the outset but with appreciable numbers of normal-sized cells. As recovery progressed clinically, accompanied by the decrease in numbers of nucleated red cells, the proportion of macrocytes decreased and that of normocytes increased, the curve becoming first plateau shaped on the right side and then monoapical. With baby I (case 5, fig 5) the number of macrocytes was so great that only a slight broadening of the base of the curve indicated the presence of normocytes on the first day of life.

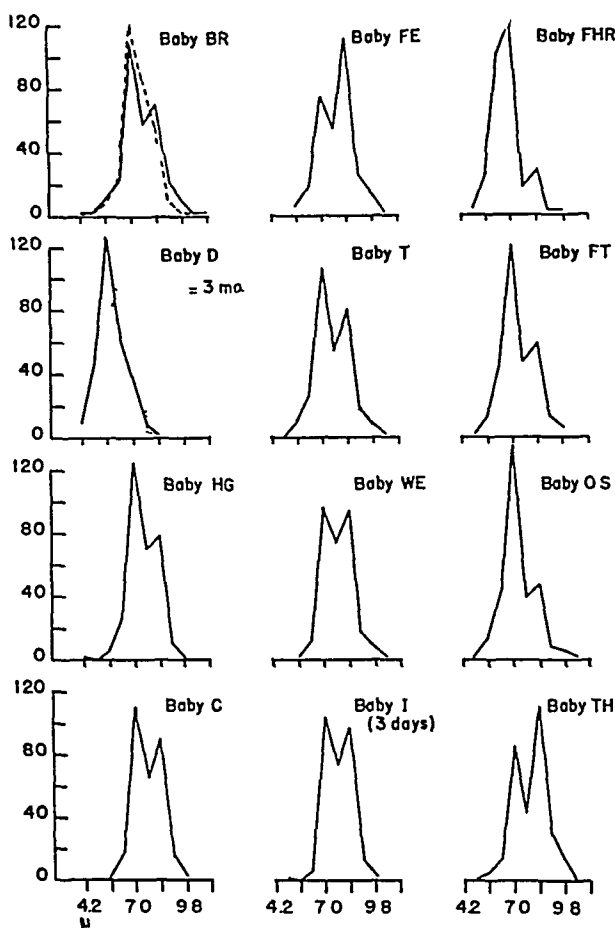


Fig 2—Price-Jones curves made on 11 infants with icterus gravis and 1 infant with unclassified erythroblastosis foetalis (baby TH). The dash line is a control curve.)

and on the second day a symmetric macrocytic curve appeared. On the succeeding day, however, there was a marked increase in the number of normocytes, and the curve became first biphasic and then monophasic and was well on the way to normal by the seventh day. Baby FT (case 6, fig 6) was not so sick as the others, and in his case the rapid restoration of a normal curve, slightly on the microcytic side, is seen by the end of a week. Baby WE (case 7, fig 7) showed a bimodal curve at the outset, with rapid increase of macrocytes and a gradual return toward

TABLE 1—Pertinent Data on the Blood of Twelve Infants with Fetal Hydrops<sup>1</sup>

	Baby	Hemo- globin, Gm /100 Cc	Erythro- cytes, Millions/ Cu Mm	Nucleated Red Cells/100 White Cells	Red Cell Diameters, $\mu$ 300 Consecutive Round Cells												Outcome and Changes Noted in Liver at Necropsy	
					4.2	4.9	5.6	6.3	7.0	7.7	8.4	9.1	9.8	10.5	11.2	11.9		12.6
W *				328	1		3	9	30	49	121	35	49	2	1			Stillborn, dense hemopoietic foci
HU		4.5	1.00	686		2	5	8	32	38	82	40	77	10	6	3	1	Died 15 min after birth, no necropsy
McK *				1,686			1	4	14	19	81	47	86	28	19	6		Stillborn, no necropsy
HE *		2.0	0.50	204		2	3	4	17	35	66	55	76	24	16	2		Stillborn, numerous hemopoietic foci
N *		2.8	0.57	140	1		4	7	10	35	69	59	76	25	17	5	1	Stillborn, many hemopoietic foci, fibrosis
PH *		4.6	1.27	980			1	2	6	17	52	31	85	53	42	13	9	Died, hemopoietic foci, bile pigment, fibrosis
F *				166		1	18	51	120	34	51	13	8	4				Died, many hemopoietic foci, iron pig- ment
S		22.8	6.00	102		2	7	21	84	69	86	22	14	3	1			Recovered
PL *				190			2	10	95	85	95	17	10	2				Stillborn, hemopoietic foci
SC		13.6	1.80	370			4	27	122	69	83	11	7					Died 2 hr after birth, no necropsy
FL		16.0	4.20	214	1	1	1	5	56	51	121	38	20	4	1	1		Recovered
B		12.0	4.00	51		2	5	18	93	67	100	19	7	1				Recovered

\* Six hundred cells were counted

normal. A sixth infant, baby C (case 8, fig 8), was observed until death, which occurred on the third day of life. His curve was biphasic at first but then shifted to the left after a transfusion. Simultaneously, he became more icteric, and the blood count failed to rise. The clinical

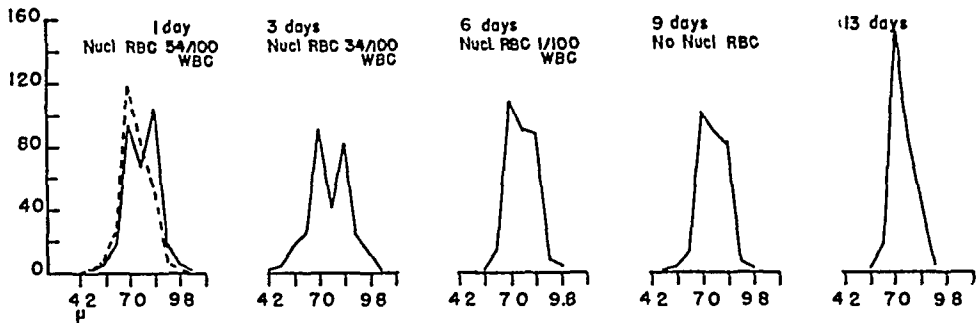


Fig 3—Serial Price-Jones curves made on baby B

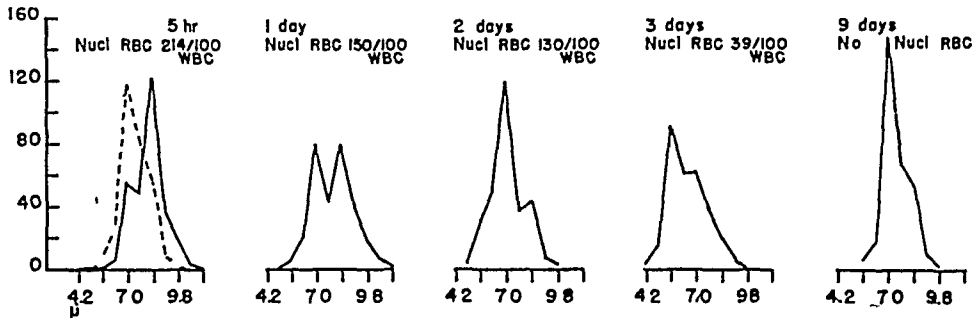


Fig 4—Serial Price-Jones curves made on baby FL

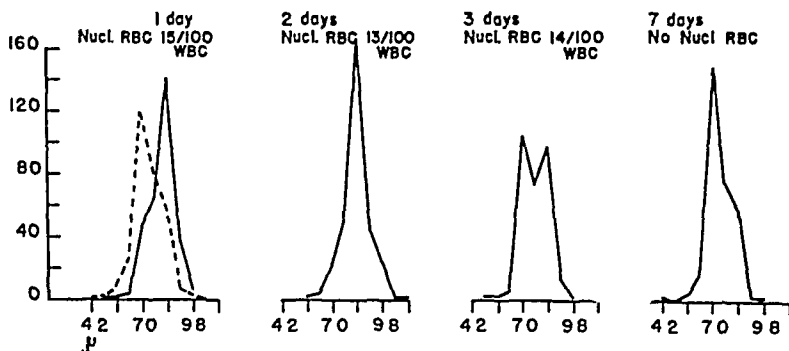


Fig 5—Serial Price-Jones curves made on baby I

picture was that of increased hemolysis, of which the leftward shift of the curve was also an indication.

The control studies showed an average red cell count on cord blood of 5,078,000 and an average hemoglobin level of 15.6 Gm per hundred cubic centimeters, as compared with values of 6,134,000 and 20.3 Gm, respectively, obtained on the same infants four hours later. This marked difference was attributed to dehydration. The Price-Jones



TABLE 2—*Patient Data on the Blood of Eleven Infants with Icterus Gravis and One Unclassified Infant*

Baby	Hemo globin, Gm./100 Cc	Erythro- cytes, Millions/ Cu Mm	Nucleated Red Cells/100 White Cells	Red Cell Diameters, $\mu$ 300 Consecutive Round Cells												Outcome and Changes Noted in Liver at Necropsy															
				42	49	56	63	70	77	84	91	98	105	112	119		126														
BR			98	1	2	9	22	108		57	70	20	11	1																	Stillborn hemopoietic foci
FL	14.0	3.90	52			7	19	71		53	110	26	15	1																	Stillborn, hemopoietic foci
FHR	6.0	1.40	235			4	27	100	121	18	27	3	1																		Recovered
D *	10.8	3.10	6	9	48	130	63	40	9	1																					Recovered
3 mo later			0		3	66	105	122	5	1																					Recovered
T	16.5	5.30	40		1	10	25	105	55	80	17	8	1																		Recovered
FT	18.5	6.50	28		3	12	14	120	47	57	12	7																			Recovered
HG	17.1	7.00	47	1		6	26	125	72	78	11	3																			Stillborn, numerous hemopoietic foci
WL	17.5	5.00	50			2	12	97	75	94	19	8	1																		Recovered
O'S *	7.3	1.30	362		1	15	45	138	10	15	8	6	2																		Recovered
C	13.0	2.70	5			1	18	110	67	90	16	4																			Died 3rd day, numerous hemopoietic foci
I (3rd day)	13.2	3.52	14		1	1	7	103	73	96	15	4																			Recovered
TH	20.0	6.30	500		1	6	14	84	18	110	31	15	2																		Died 1st day, marked necrosis of liver

\* Six hundred cells were counted

30 babies less than 48 hours old, and is less than van Creveld's figure of 80 microns.<sup>8</sup> The mean cell diameter of the cord blood was 7.47 microns and of the peripheral blood 7.41 microns.

In the 12 control curves (fig 9), although several of the patients showed marked anisocytosis, the distribution was usually fairly uniform, and in no case was the curve biphasic.

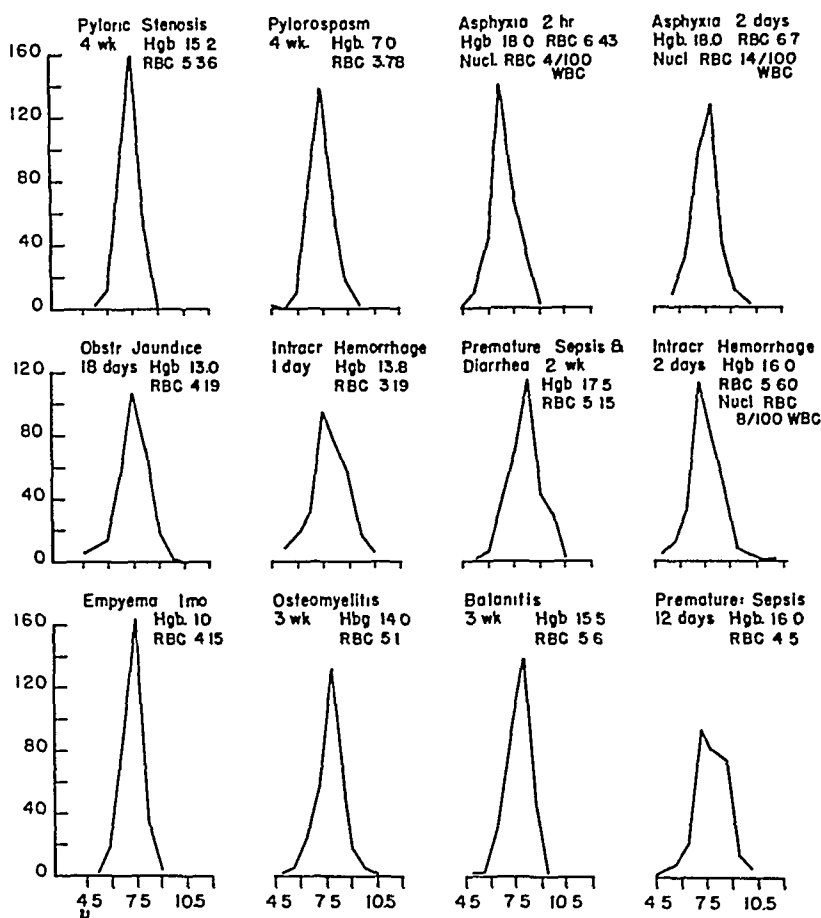


Fig 9—Price-Jones curves made on 12 infants aged 2 hours to 1 month, suffering from a variety of conditions.

#### COMMENT

From the foregoing material it became evident that patients with erythroblastosis exhibited morphologic alterations in the red cells of the same general type as those seen in clinical and in experimental auto-hemolytic anemias. In 23 cases the Price-Jones curves were biphasic with macrocytic peaks, and in 1 case (1, baby D) there was marked microcytosis. The case record of this patient aids in interpreting this curve (see appended case reports).

<sup>8</sup> van Creveld, S. Diameter of Red Blood Cells of Premature Infants and of Those Born at Full Term, *Am J Dis Child* 44:701 (Oct) 1932.

curve for the whole group (three thousand cells) was monoapical, with a definite broadening of the base. Curves done on combined cord blood smears and peripheral blood smears coincided closely. The mean cell

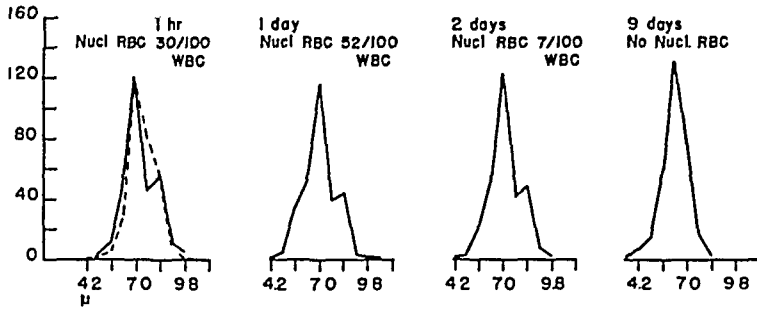


Fig 6—Serial Price-Jones curves made on baby FT

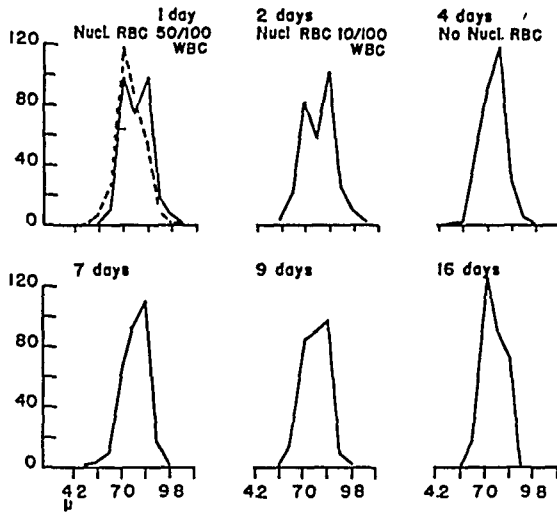


Fig 7—Serial Price-Jones curves made on baby WE

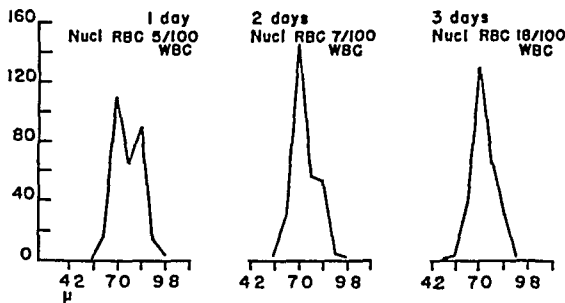


Fig 8—Serial Price-Jones curves made on baby C

diameter for the three thousand cells was 7.44 microns, which coincides closely with Silvette's figure of 7.45 microns,<sup>7</sup> for six thousand cells in

<sup>7</sup> Silvette, H. A Study of Erythrocyte Diameters in the Newborn, *J Lab & Clin Med* **13** 245, 1927

larger than the red cells into which they mature,<sup>11</sup> and undoubtedly they account for part of the macrocytic cells in the present cases. However, there is a wide discrepancy between the number of macrocytes predictable from the reticulocyte percentage plus the normal expectancy, and the actual numbers. For example, in the curve illustrated in figure 10 *B* the reticulocyte percentage was 6.7, or twenty of three hundred cells. The expected number of red cells 8.4 microns in diameter in a homogeneous cell population of normal mean diameter has not been calculated. However, it can be readily seen that it should be such that when added to the number of reticulocytes the total number of cells 8.4 microns in diameter would be far less than that observed, ninety.

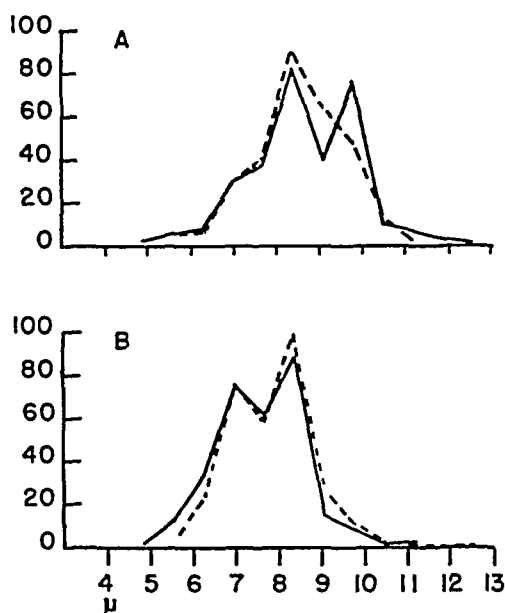


Fig 10—Price-Jones curves (three hundred cells each) made on erythrocytes (solid line) and reticulocytes (dotted line) of 2 infants with erythroblastosis foetalis

Moreover, if the macrocytosis is due to reticulocytes, distribution curves done on reticulocytes should show more macrocytosis than those done on mature red cells. Therefore, on two smears available in which the reticulocytes were sufficiently numerous to count, such comparative Price-Jones curves were made in the usual fashion. The results (fig 10 *A* and *B*) show that the reticulocytes do not follow the anticipated distribution. It is likely that in some of the milder cases with small macrocytic peaks the peaks represent reticulocytes, but in more severe cases another explanation must be sought.

11 Persons, E. L. Studies of Red Blood Cell Diameter. III. The Relative Diameter of Immature (Reticulocytes) and Adult Red Blood Cells in Health and Anemia, Especially in Pernicious Anemia, *J Clin Investigation* 9:615, 1929.

The true nature of the illness of baby D was brought out by the transfusion with paternal blood, which, in the light of present knowledge, probably contained antigens against which the infant's blood had antibodies, transmitted to it diaplacentally by the mother. The resulting hemolysis was attested to by the fall in blood count and the rise in icteric index after transfusion. At this time (Oct 3, 1937) the Price-Jones curve showed a marked shift to the left (fig 2). The mean cell volume at the same time was 109.8 cubic microns, from which one may conclude that the cells were smaller and rounder, and the smear revealed the presence of spherical microcytes with hyperchromatic centers in contrast to the central pallor of the normal erythrocytes present. Spherocytes are more fragile in hypotonic solution of sodium chloride, and this is reflected in the results of fragility tests done on this patient. Whipple<sup>21</sup> has recently shown that the cause of splenic enlargement in experimental hemolytic anemia in animals is that the spherocytes, because of their increased volume, cannot pass through the stomas of the splenic venous sinuses freely. This may explain the marked splenomegaly suddenly appearing at this time in this patient. Finally, when another donor was used, the patient made a gradual recovery and at the end of three months had a normal red cell diameter, blood count, icteric index and red cell fragility. From these facts the possibility of this being a case of familial hemolytic icterus seems definitely excluded. Whether the pathologic cerebral condition later uncovered was in any way related to the icterus gravis is pure speculation in the absence of autopsy evidence of nuclear bile staining (kernikterus).

Any natural property of a homogeneous population can be expressed as a function of two dependent variables,  $x = (f) y$ . This gives a simple binomial curve in the shape of a parabola. The more cells one counts the closer the observed curve will coincide with the expected curve of variation. When the observed curve, however, coincides only slightly or not at all with the expected curve, one may assume that one is dealing with a heterogeneous population. Thus, the foregoing observations indicate the presence of three races of cells, each following a homogeneous pattern: e.g. microcytes, normocytes and macrocytes. Obviously, to speak of a mean cell diameter in such a group is meaningless.<sup>9</sup>

In analyzing the macrocytic curves more closely the main question was the nature of the macrocytes. The accepted view is that they are reticulocytes and immature cells which are called forth in response to destruction of blood.<sup>10</sup> Reticulocytes are known to be about 1 micron

9 Price-Jones, C. The Diameters of Red Cells in Pernicious Anemia and in Anemia Following Hemorrhage, *J. Path. & Bact.* **22** 487, 1922.

10 Wintrobe, M. M. Relation of Variations in Mean Corpuscular Volume to Number of Reticulocytes in Pernicious Anemia, *J. Clin. Investigation* **13** 669, 1934. Dameshek and Schwartz.<sup>11</sup> Tigertt and Duncan.<sup>22</sup>

The significance of megaloblasts is still a subject of controversy, but at present a majority of investigators in this country and Europe incline to the opinion that they represent an abnormal type of erythropoiesis which occurs in the absence of the hepatic erythrocyte maturation factor.<sup>16</sup> The presence of megaloblasts in these smears may similarly point to hepatic insufficiency as the major contributory cause of the macrocytosis in the cases with high macrocytic peaks. This is not unexpected in view of the many other evidences of hepatic damage in erythroblastosis foetalis.

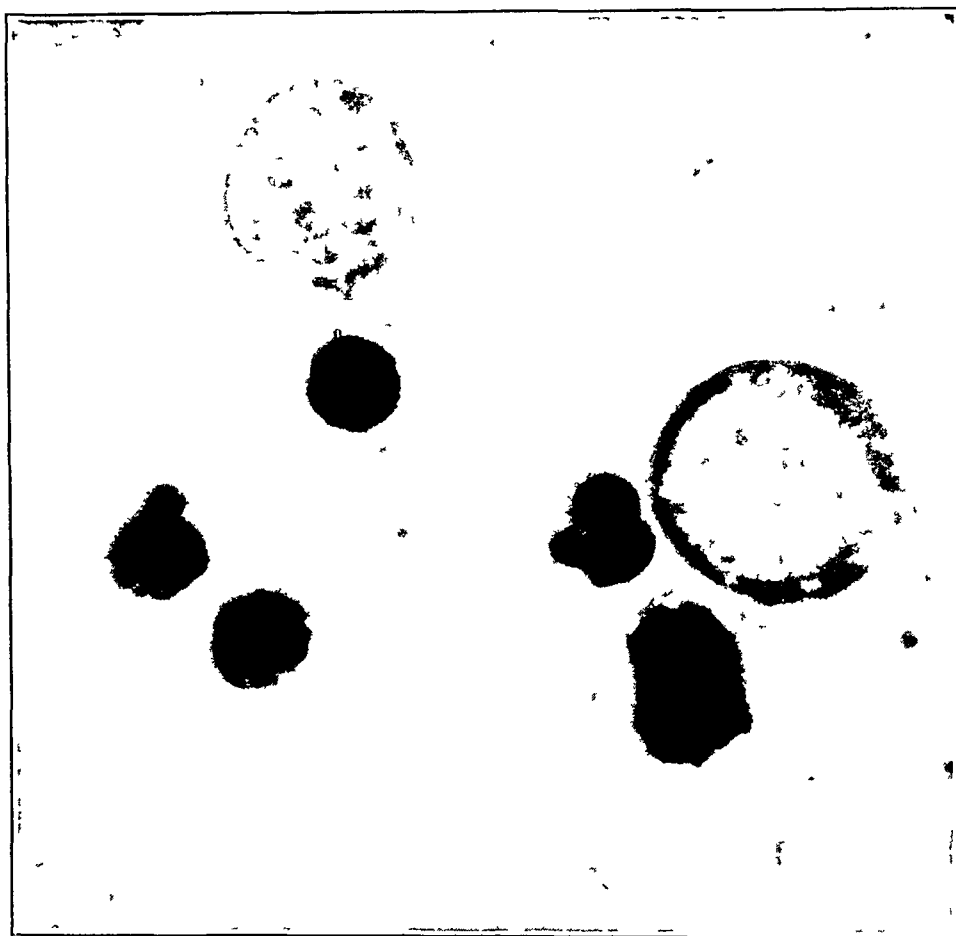


Fig 11—A smear of the cord blood of baby McK, showing several nucleated red cells and two megaloblasts (Wright's stain,  $\times 1,800$ )

Other authors have previously incriminated the liver. Javerit showed that his patients with hydrops had extremely low levels of plasma proteins, prothrombin and fibrinogen. The van den Berg reaction in erythroblastic patients is biphasic or direct. Numerous necropsy reports indicate

<sup>16</sup> Kato, K. Monophyletic Scheme of Blood Cell Formation for Clinical and Laboratory Reference, *J Lab & Clin Med* **20** 1243, 1935. Israels, M C G. The Pathological Significance of the Megaloblast, *J Path & Bact* **49** 231, 1939. Wintrobe, M M. *Clinical Hematology*, Philadelphia, Lea & Febiger, 1942, p. 59. Dameshek and Valentine.<sup>5</sup> Jones.<sup>6</sup>

The degree of reticulocytosis in erythroblastosis foetalis reported by different authors varies. In Diamond, Blackfan and Baty's<sup>12</sup> series it was 8 to 20 per cent, Hawksley and Lightwood<sup>13</sup> reported figures ranging between 3 and 11.9 per cent on the initial smear, Vogel<sup>14</sup> reported 5 to 30 per cent, and in the cases reported by Javert<sup>15</sup> it averaged 7.1 per cent. It appears that the degree of reticulocytosis is not as high as one usually encounters in other hemolytic anemias with a comparable degree of blood destruction, and the possibility of marrow inhibition must be considered. In the presence of macrocytosis the cause of inhibition might theoretically be a lack of the erythrocyte maturation factor stored in the liver.

To investigate this point differential counts were made on the nucleated red cells in the smears of 6 patients with severe erythro-

TABLE 3—*Differential Counts for Nucleated Red Cells (One Hundred Cells) for Six Infants with Severe, Fatal Erythroblastosis Foetalis*

Baby	Hemoglobin, Gm./100 Gm.	Erythrocytes, Millions/ Cu. Mm.	Nucleated Red Cells/100 White Cells	Proerythroblast	Megaloblast A	Megaloblast B	Normoblast A	Normoblast B	Orthochromatic Mixed Group	Changes Noted in Liver at Necropsy
W			328		1	22	1	22	54	Densely packed hemopoietic foci
F			166	2	4	7	1	9	77	Many hemopoietic foci, brown pigment
HE	2.0	0.50	204	2	10	16	8	10	54	Numerous hemopoietic foci
TH	20.0	6.30	500	3	8	13	4	10	62	Extensive hemorrhagic necrosis, hemopoiesis
HU	4.5	1.00	686	3	3	14	13	16	50	No autopsy
McK			1,686	3	10	12	7	21	47	No autopsy

blastosis, all of whom died. The results have been tabulated (table 3). In all cases unmistakable megaloblasts were observed (fig 11). Four of the 6 patients were examined at autopsy, and all of them showed varying degrees of hepatic damage, ranging from crowding of the hepatic parenchyma by extramedullary hemopoietic centers to extensive hemorrhagic necrosis (fig 12), cellular infiltration, fibrosis and heavy deposits of iron and of bile pigment.

12 Diamond, L. K., Blackfan, K. D., and Baty, J. M. Erythroblastosis Foetalis and Its Association with Universal Edema of the Fetus, Icterus Gravis Neonatorum and Anemia of the Newborn, *J. Pediat.* **1**: 269, 1932.

13 Hawksley, J. C., and Lightwood, R. A Contribution to the Study of Erythroblastosis Icterus Gravis Neonatorum, *Quart. J. Med.* **27**: 155, 1934.

14 Vogel, P. Clinical and Hematological Aspects of Erythroblastosis Foetalis, read at a meeting of the New York Pathological Society, New York Academy of Medicine, Jan. 22, 1942.

15 Javert, C. T. Erythroblastosis Neonatorum, *Surg., Gynec. & Obst.* **74**: 1, 1942.

Darrow<sup>4</sup> suggested that the observed hepatic damage could be explained on the basis of a hypothetic antigen-antibody reaction, citing the work of Weil<sup>19</sup> and Dean and Webb,<sup>20</sup> who studied the changes in the liver in dogs during anaphylactic shock. Darrow expressed the opinion that the erythroblastemia might be at least partly attributable to increased hemopoietic activity in response to lower arterial oxygen tension due to hepatic damage.<sup>21</sup> Dean and Webb<sup>22</sup> showed that within two minutes after anaphylactic shock had been produced in the dog the number of nucleated erythrocytes in the blood underwent a marked increase, as much as forty times the normal number. In a case of anaphylaxis in man<sup>23</sup> Dean reported extensive hemorrhage and necrosis in the liver. More recently Hartley and Lushbaugh<sup>24</sup> have shown that focal necrosis of the liver can be produced in sensitized rabbits and guinea pigs by injecting sublethal doses of antigenic serum. While these facts have a suggestive bearing on the present problem, it is wise to be cautious in applying them to human pathology. It remains to be shown whether focal necrosis occurs in the livers of animals given hemolyzing antiserum. In a patient with an autohemolytic anemia Farrar and associates<sup>25</sup> observed severe hepatic damage, which improved when the spleen was removed and hemolysis presumably stopped.

Since the discovery of the role of the liver in the pathogenesis of pernicious anemia many observers have reported the presence of macrocytic anemia as an accompaniment of various types of hepatic disease.<sup>25</sup>

19 Weil, R. Anaphylaxis in Dogs. A Study of the Liver in Shock and in Peptone Poisoning, *J Immunol* **2** 525, 1917.

20 Dean, H. R., and Webb, R. A. The Morbid Anatomy and Histology of Anaphylaxis in the Dog, *J Path & Bact* **27** 51, 1924.

21 Judd, E. S., Snell, A. M., and Hoerner, M. T. Transfusion for Jaundiced Patients, *J A M A* **105** 1653 (Nov 23) 1935.

22 Dean, H. R., and Webb, R. A. The Blood Changes in Anaphylactic Shock in the Dog, *J Path & Bact* **27** 65, 1924.

23 Dean, H. R. The Histology of a Case of Anaphylactic Shock Occurring in a Man, *J Path & Bact* **25** 305, 1922.

24 Hartley, G., and Lushbaugh, C. C. Experimental Allergic Focal Necrosis of the Liver, *Am J Path* **18** 323, 1942.

25 Schulten, H., and Malamos, B. Ueber Veränderungen der roten Blutkörperchen bei Lebererkrankungen, *Klin Wchnschr* **11** 1338, 1932. Fellingner, K., and Klima, R. Untersuchungen über Anämien bei Leberzirrhosen, *Wien klin Wchnschr* **46** 1191, 1933. Gamma, C. Ueber Veränderungen der roten Blutkörperchen bei Lebererkrankungen, *Klin Wchnschr* **12** 348, 1933. Cheney, G. The Morphology of the Erythrocytes in Cirrhosis and Other Disorders of the Liver, *California & West Med* **39** 90, 1933. van Duyn J., Jr. Macrocytic Anemia in Disease of the Liver, *Arch Int Med* **52** 839 (Dec) 1933. Wright, D. O. Macrocytic Anemia and Hepatic Cirrhosis, *Am J M Sc* **189** 115, 1935. Rosenberg, D. H., and Walters, A. Macrocytic Anemia in Liver Disease, Particularly Cirrhosis, *ibid* **192** 86, 1936. Wintrobe, M. M. Relation of Disease of the Liver to Anemia, *Arch Int Med* **57** 289 (Feb) 1936. Schalm, L. The Average Red Blood Cell Diameter in Liver Disease and Jaundice, *Acta med Scandinav* **93** 513, 1938.



extensive hepatic damage<sup>17</sup> in cases of hydrops. In these there is usually extensive and often almost complete necrosis of the hepatic parenchyma, whereas in milder cases of icterus gravis there is less severe necrosis, and in the mildest ones there are only slight evidences of hepatic cellular damage. Varying degrees of extramedullary hemopoiesis are observed in the liver in all types. Several cases of portal cirrhosis in children who had recovered from icterus gravis neonatorum are reported in the literature<sup>18</sup>

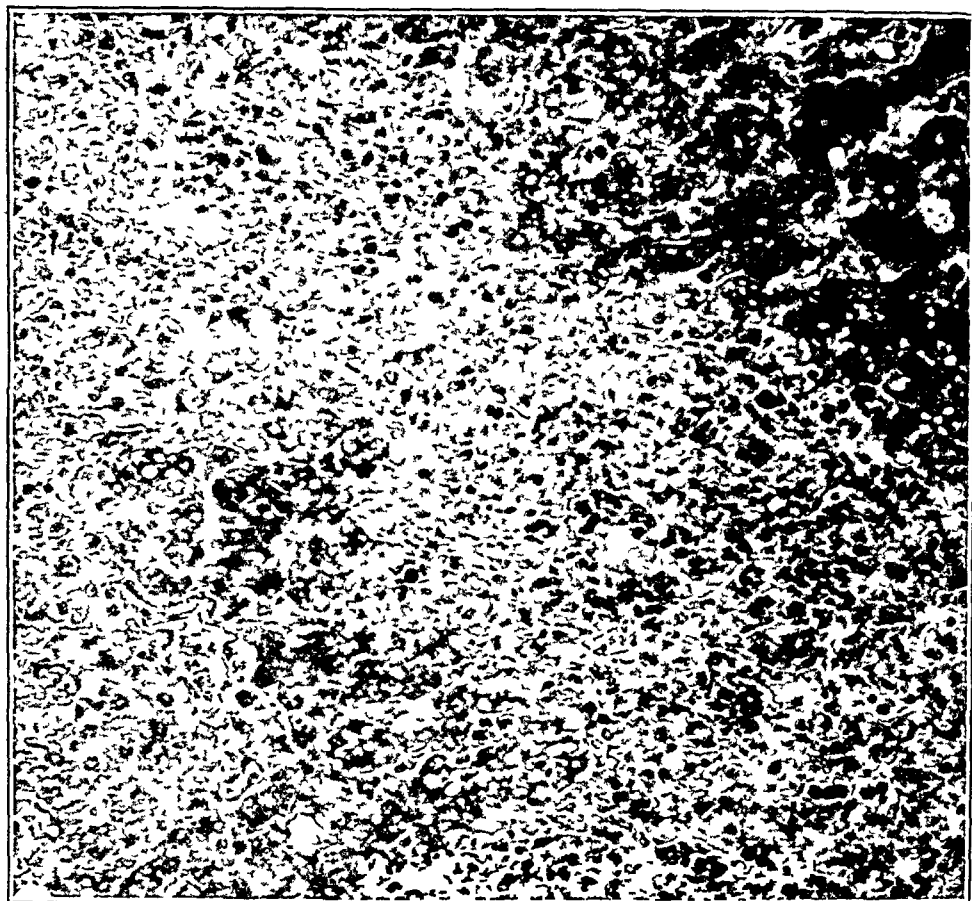


Fig. 12—A section of the liver of baby TH, showing severe hemorrhagic necrosis, extramedullary hemopoiesis and hepatic cellular degeneration (Hematoxylin and eosin,  $\times 450$ )

17 Polayes, S. H. Pathology of Erythroblastosis Fetalis, read at a meeting of the New York Pathological Society, New York Academy of Medicine, Jan 22, 1942. Parsons, L. G., Hawksley, J. C., and Gittins, R. The Hemolytic (Erythronoclastic) Anemias of the Newborn Period with Special Reference to Erythroblastosis of the Newborn, *Arch. Dis. Childhood* 8:159, 1933. Diamond, Blackfan and Baty<sup>12</sup>. Hawksley and Lightwood<sup>13</sup>. Javert<sup>15</sup>.

18 Braid, F., and Ebbs, J. H. Atrophic Cirrhosis of the Liver Following Icterus Gravis Neonatorum, *Arch. Dis. Childhood* 12:389, 1937.

against them are produced. These antibodies are transmitted diaplacentally to the fetus in which an antigen-antibody reaction takes place. Hemolysis occurs, accompanied or followed by damage to the liver and perhaps to other organs. During the phase of hemolysis the blood cells probably become smaller and spheroid in shape, but since this reaction occurs *in utero* it cannot be demonstrated clinically. Soon there is an admixture of larger new cells in the blood stream which arise in the marrow and the extramedullary hemopoietic centers. If the degree of hepatic damage is severe, adequate fetal supplies of erythrocyte maturation factor are not available and megaloblastic erythropoiesis takes place. The less mature the fetus the more marked this reaction is likely to be. Javeit<sup>15</sup> has shown that babies with hydrops are usually premature, while the babies with icterus gravis are more likely to be full term. This may be the explanation for the generally larger cell diameters observed in some of our cases of hydrops (fig. 1). Babies with strong antigen-antibody reactions may have more severe hepatic damage and present the clinical picture of fetal hydrops, those with less severe reactions have icterus gravis, and those with the least severe reactions show only the effect of the blood destruction and their condition is called congenital anemia of the newborn.

The possible implications of this work for therapy are apparent, but too much should not be expected from liver therapy in patients with erythroblastosis. According to most observers, the macrocytic anemias of hepatic disease do not respond well to injection of liver extract, although Goldhamer and associates<sup>33</sup> have reported 2 cases of macrocytic anemia in cirrhosis of the liver in which the response was good. Their work suggested that acute hepatic damage may interfere with the proper utilization of liver extract, aside from its possible effect on the storage of the erythrocyte maturation factor. Bernheim-Karrer and Grob<sup>34</sup> fed large amounts of liver during the last ten weeks of pregnancy to a woman who had previously borne 2 erythroblastotic infants. The infant was born with a normal blood count and only mild icterus. Javeit, on the other hand, has tried administering injections of liver extract to mothers ante partum, without affecting the outcome. Other authors have also tried liver therapy<sup>35</sup>. It must be remembered that the blood destruction going on simultaneously with impaired regeneration in erythroblastosis militates against successful liver therapy. However, it

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33 Goldhamer, S. M., Isaacs, R., and Stungis, C. C. The Role of the Liver in Hematopoiesis, *Am J M Sc* **188** 193, 1934.

34 Bernheim-Karrer, J., and Grob, M. Zur Prophylaxe des Icterus Neonatorum Gravis, *Ztschr f Kinderh* **50** 672, 1930.

35 Cooley, T. B. Round Table Conference on Diseases of the Blood and Hematopoietic System, *J Pediat* **1** 635, 1932. Clifford, S. H., and Hartig, A. T. Erythroblastosis of the Newborn, *New England J Med* **207** 105, 1932. Hampson, A. C. Jaundice in the Newly Born, *Practitioner* **131** 59, 1933.

Macrocytosis has also been reported in animals with experimentally produced hepatic damage<sup>26</sup> Briese<sup>27</sup> administered carbon tetrachloride vapor to pregnant rats during their gestation period and observed a slightly larger cell diameter and volume and a lower red cell count in the offspring, which she attributed to the impairment of the maternal supply of erythrocyte maturation factor

Wintrobe and Shumacker<sup>28</sup> showed that the red cells in the maturing fetus exhibit changes similar to those of red cells in a person with pernicious anemia undergoing liver therapy, e g, decreasing size and increasing number This work was confirmed by Nishida<sup>29</sup> From this Wintrobe and Shumacker postulated that as the fetal liver matured, more erythrocyte maturation factor was available for hemopoiesis Since then various contradictory reports as to the effect of liver extract on the cells of developing embryos have been made, but two recent studies by Stasney and Burns<sup>30</sup> and Jones<sup>31</sup> indicate that the maturation of fetal red cells may be accelerated by the administration of both liver and gastric juice

With this review of clinical and experimental facts it is perhaps permissible to formulate a tentative explanation for the observations reported in this paper Bearing in mind that the final word has not yet been said on the subject of the Rh factor, one may assume that the fetal blood in erythroblastosis foetalis contains antigens, inherited from the father, which the mother lacks One of these is Rh, another is hR, and there are probably others as yet undiscovered Through a defect in the placenta fetal red cells enter the maternal circulation,<sup>32</sup> and antibodies

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26 Wintrobe, M M, and Shumacker, H B Morphologic Changes in the Blood Associated with Experimentally Produced Hepatic Damage, *J Clin Investigation* **15** 455, 1936 Rodriguez-Molina, R Experimental Liver Damage Associated with Hematological Changes in Hogs, *Puerto Rico J Pub Health & Trop Med* **15** 362, 1940 Higgins, G M, and Stasney, J The Peripheral Blood in Experimental Cirrhosis of the Liver, *Folia haemat* **54** 129, 1934

27 Briese, E The Effect on the Blood Cells of the Fetal Rat Produced by the Inhalation of Carbon Tetrachloride by the Mother During Gestation, *Am J M Sc* **195** 787, 1938

28 Wintrobe, M M, and Shumacker, H B Comparison of Hematopoiesis in the Fetus and During Recovery from Pernicious Anemia, *J Clin Investigation* **14** 837, 1935

29 Nishida, K Entwicklungsgeschichtliche Studie über die Blutbildung des japanischen Embryos II Messung des Erythrozytendurchmessers in der Leber des Embryos, *Nagasaki Igakkwai Zasshi* **17** 929, 1937

30 Stasney, J, and Burns, E L Influence of Active and Inactive Antianemic Principles upon the Erythrocytes of the Immature Opossum, *Am J M Sc* **203** 191, 1942

31 Jones, O P Transmission of Antianemic Principle Across the Placenta and Its Influence on Embryonic Erythropoiesis Quantitative Effects of Diet Containing Ventriculin, *Arch Int Med* **68** 476 (Sept) 1941

32 Javert has recently demonstrated hematomas in the placentas of erythroblastic infants (Further Studies on Erythroblastosis Neonatorum of Obstetric Significance, *Am J Obst & Gynec* **43** 921, 1942)

*Physical Examination*—On admission the positive physical findings were poor activity and cry, moderate icterus and clonic twitches of the eyelids. The head and the chest both measured 34.5 cm. The eyes were somewhat slitlike, but there were no other signs suggestive of mongolism. The conjunctivas were pale and the scleras icteric. The heart and lungs were normal. The edge of the liver was palpable 1 cm below the costal margin. The reflexes were hyperactive. The spleen was not palpable.

*Laboratory Data*—The results of laboratory examinations of the blood have been tabulated as follows:

Blood count	Date	Hemoglobin, Gm /100 Cc	Red Cells	Nucleated Red Cells per 100 White Cells	
				White Cells	Cells
	9/30/37	12.0	3,480,000	11,240	1
	10/3/37			26,000	3
	10/4/37	10.8	3,100,000	28,200	6
	10/13/37	12.6	4,580,000		0
	8/9/38	13.0	5,850,000		
Icteric index	Date	Value			
	9/30/37	125			
	10/4/37	150			
	10/13/37	34			
	10/21/37	9			
Mean cell volume	10/3/37	109.8 cu mm			
Reticulocytes	10/15/37	7%			
	Date	Patient		Control	
		Beginning Hemolysis	Complete Hemolysis	Beginning Hemolysis	Complete Hemolysis
Red cell fragility in	10/5/37	0.50	0.36	0.42	0.32
hypotonic solution	10/6/37	0.60	0.34	0.42	0.26 <sup>a</sup>
of sodium chloride	10/13/37	0.44	0.34	0.44	0.26 <sup>b</sup>
	8/11/38	0.46	0.36	0.46	0.36
Culture	10/1/37	No growth			
Kline reaction	10/1/37	Negative			

These control values show an unusually low level of complete hemolysis and may represent errors in technic. It is felt that they could not rightfully be omitted, however, and I do not believe they impair the significance of the values obtained with the patient's blood.

*Course of Illness*—On the day of admission and on the following day the patient was transfused with blood of her father. After the second transfusion, the temperature rose, she became deeply jaundiced and the liver and the spleen enlarged so that they were palpable 2 cm and 5 cm respectively below the costal margin. This condition persisted for several days, during which time several additional transfusions were given with a different donor. After this the icterus disappeared and the patient made an uneventful recovery and was discharged on October 25. In August of the following year (Aug 11, 1938) she was readmitted with convulsive seizures and failure to develop properly. On this admission an air encephalogram showed cerebral cortical atrophy. The blood

seems reasonable to suggest injections of liver extract as an adjuvant to transfusion therapy, particularly during the recovery phase in patients with this disease

Finally, the question is raised whether hepatic damage may play a role in the production of other macrocytic hemolytic anemias in human beings or in animals <sup>36</sup>

#### SUMMARY

Price-Jones curves were made on cord blood or peripheral blood in 12 cases of fetal hydrops and 12 cases of icterus gravis at the onset of illness. In 23 cases a characteristic biphasic curve, consisting of a normocytic and a macrocytic peak or two macrocytic peaks, was observed. In 1 case a monophasic microcytic curve was observed. A blood smear in this case revealed the presence of spherical microcytes, but three months later the smear was normal.

The morphologic changes in erythrocytes in erythroblastosis foetalis resemble in some respects, those observed in experimental hemolytic anemias due to antigen-antibody reactions.

Examination of blood smears in 6 cases of severe erythroblastosis foetalis revealed varying numbers of megaloblasts. Postmortem examination in 4 cases revealed varying degrees of hepatic damage. The suggestion is made that the presence of megaloblasts and the macrocytosis, in part at least, may be the result of deficient erythrocyte maturation factor due to hepatic damage.

The blood destruction in this disease is believed to be best explained on the basis of an antigen-antibody reaction in the fetus, as suggested by other investigators. It is suggested that the hepatic damage may possibly be due to the same cause.

#### REPORT OF EIGHT CASES

**CASE 1 (fig 2)**—Baby D, Jewish, was hospitalized from September 30 to Oct 25, 1937.

**Family History**—The mother, aged 29, had had a thyroidectomy for exophthalmic goiter several years previously. In 1936 she had borne a normal infant, who was living and well. There was no history of jaundice in either side of the family.

**Past History**—The patient had been born one week before the expected date and weighed 4,000 Gm.

**Present Illness**—At birth the infant had been moderately icteric, and the jaundice persisted until admission. On the sixth day of life she was listless and feeble. The next day twitchings of the eyelids and the mouth were observed, and she was transferred to the pediatric ward.

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<sup>36</sup> Dyke, S. C., and Young, F. Macrocytic Hemolytic Anaemia Associated with Increased Cell Fragility, *Lancet* **2** 817, 1938. Lambie, C. G. Macrocytosis in Hereditary Hemolytic Anemia (Alcoholic Jaundice) with Report of a Case, *M. J. Australia* **2** 285, 1938. Watson, C. J. Hemolytic Jaundice and Macrocytic Hemolytic Anemia. Certain Observations in Series of Thirty-Five Cases, *Ann. Int. Med.* **12** 1782, 1939.

*Physical Examination*—Marked icterus of skin, cord and scleras was present. The skin appeared generally puffy but did not pit on pressure. It was covered with scattered fine petechiae. The liver was palpable 3 cm below the costal margin, and the spleen, 2 cm below the costal margin.

*Laboratory Data*—The results of laboratory examination have been tabulated as follows:

Urine on admission	
Color	Reddish brown
Albumin	++
Red cells per high power field	10-65
White cells	Occasional
Granular cells	Occasional
Blood count	
Hemoglobin, Gm/100 cc	12.0
Red cells	4,000,000
White cells	35,000
Nucleated red cells/100 white cells	54
Icteric index	107
Prothrombin	20%
Rh antigen	Present
Kline reaction	Negative

*Course of Illness*—For the first two days he was given daily intramuscular injections of menadione (vitamin K) in oil and blood transfusions. The blood count did not rise, the number of nucleated red cells increased slightly, and the icterus deepened. Two more transfusions from another donor were given, and the number of red cells and the hemoglobin level increased and stayed up, and the nucleated red cells diminished in number and were not seen after February 15. Meanwhile, however, the jaundice deepened, the urine began to give a positive reaction for bile and the stools became light in color. On February 19, the icteric index was 250 and the van den Bergh reaction was positive (immediate direct). After two weeks, the icterus gradually diminished, the urine became bile free and the stools became normally pigmented. Recovery was retarded by an infectious diarrhea which was treated with sulfadiazine (2-[paraaminobenzenesulfonamido]-pyrimidine). Just before discharge the icteric index was 125, prothrombin was 57 per cent, and bromsulphalein dye was absent from the blood thirty minutes after injection. The hemoglobin level was 13.5 Gm per hundred cubic centimeters, and the red cell count was 3,580,000 on discharge on April 14.

CASE 4 (fig 4)—Baby FL, Irish, was hospitalized from October 4 to Nov 16, 1941.

*Familial History*—The mother, aged 31, was living and well, and her blood did not contain Rh antigen. The father's blood contained this antigen. The first sibling was living and well. Three siblings had died of erythroblastosis. A fifth sibling, living and well, had been icteric at birth.

*Past History*—Pregnancy had been uneventful, lasting forty-three weeks. The mother had received menadione for two weeks before delivery. The weight at birth was 4,400 Gm.

*Present Illness*—The infant breathed poorly after birth and received 1 cc of menadione in oil<sup>37</sup> intramuscularly in the nursery. A smear of blood at birth showed erythroblastosis, and the baby was transferred to the pediatric service.

<sup>37</sup> The menadione in oil used in these cases contained 1 Gm of menadione in each cubic centimeter.

count and the red cell fragility on this admission were normal. Since her discharge on that admission she has not been seen again in the New York Hospital Children's Clinic.

CASE 2 (fig 2)—Baby TH, Negro, was hospitalized Jan 26 and 27, 1942.

*Familial History*—The father, aged 33, was living and well, and the Wassermann reaction of his blood was negative. The mother, aged 33, had been discovered to have a positive Wassermann reaction in the seventh month of pregnancy. Since then she had been treated with sixteen injections of arsphenamine and nine injections of a bismuth compound. Her blood did not contain Rh antigen.

*Past History*—The infant had been delivered normally at full term. The weight at birth was 2,450 Gm. The vernix caseosa was icteric. The baby was slow to breathe and was transferred directly to the pediatric ward.

*Physical Examination*—The baby's color, cry and activity were poor. Scattered petechiae were present on face, scalp and neck. The upper gum was cleft. The lungs were clear. The heart showed a soft systolic murmur. The liver and spleen were both palpable 1 cm below the costal margin.

*Laboratory Data*—The results of laboratory examinations of the blood have been tabulated as follows:

Blood count	
Hemoglobin, Gm/100 cc	20.0
Red cells	6,300,000
White cells	14,700
Nucleated red cells/100 white cells	500
Wassermann reaction, 1:4 dilution	++++
Prothrombin	< 4%
Culture	No growth

*Course of Illness*—The night of admission the chest filled with rales, and the infant was put in an oxygen tent. The next morning he had several generalized convulsions, became cyanotic and died. A roentgenogram of the long bones failed to reveal any evidence of syphilis of the bone.

*Autopsy*—The main findings at autopsy were in the liver. This organ was grossly enlarged and weighed 125 Gm. The surface was dark purple red. There was an increase of grayness in the cut section, and lobular markings were not visible. Microscopically, the hepatic cells had lost their architecture, stained faintly and often showed disintegrated nuclei. There were many red cells present in these areas. The viable liver cells present showed extreme vacuolization. There were small islands of erythropoiesis (fig 12). The anatomic diagnosis included erythroblastosis foetalis and prematurity. There was no evidence of congenital syphilis.

CASE 3 (fig 3)—Baby B, Irish, was hospitalized from February 10 to April 14, 1942.

*Familial History*—The mother, aged 37, was living and well. Her blood did not contain Rh antigen and she had anti-Rh antibodies. The father was living and well and his blood contained Rh antigen. Four siblings were living and well. There was no history of icterus.

*Past History*—The infant had been delivered normally at full term, after a normal pregnancy. The weight at birth was 3,650 Gm.

*Present Illness*—On arrival in the nursery the infant was noted to be icteric and became more so during the next seven hours. A smear of blood showed numbers of erythroblasts, and the infant was transferred to the pediatric service.

performed in another hospital, was said to reveal atelectasis. There was no mention of erythroblastosis.

*Past History*—The infant was delivered by cesarian section three weeks after the expected date of confinement. The baby breathed and cried poorly and was transferred to the pediatric service immediately after birth.

*Physical Examination*—The infant was small, weighing 2,550 Gm, with a good cry, no cyanosis and normal respirations. The skin had an icteric tint, and there was slight edema of the eyelids. The edge of the liver was palpable 0.5 cm below the costal margin, the spleen was not palpable.

*Laboratory Data*—A blood count revealed 18.0 Gm of hemoglobin per hundred cubic centimeters, 6,400,000 red cells, 16,000 white cells and 32 nucleated white cells. The next day the hemoglobin content remained the same, but the red cell count had fallen to 4,600,000, the white cell count had increased to 20,000 and there were 60 nucleated red cells per hundred white cells. The blood contained hR antigen.

*Course of Illness*—After a single transfusion of blood the nucleated red cells fell to 6 per hundred white cells and then disappeared entirely, and the smear, which had showed marked anisocytosis and polychromasia, became normal. The icterus disappeared after the third day, and the baby was discharged from the nursery on February 18.

CASE 7 (fig 7)—Baby WE, American, was hospitalized from April 23 to May 22, 1942 (he was still in the hospital when this report was prepared).

*Familial History*—The mother, aged 34, was living and well and did not have Rh antigen in her blood. The father, aged 36, was living and well and had Rh antigen. The mother had had a miscarriage at three months in 1932. One sibling, who was living and well, had been icteric for several days after birth in 1933. One sibling had died of erythroblastosis foetalis in 1940.

*Past History*—Pregnancy and delivery had been normal. The mother had received menadione for several weeks prior to delivery. The infant's weight at birth was 3,340 Gm.

*Present Illness*—Because of the family history the infant was transferred directly from the delivery room to the pediatric ward.

*Physical Examination*—Positive findings on admission included a soft blowing systolic murmur at the apex of the heart and a liver palpable 2 cm and a spleen palpable 1 cm below the costal margin. There was no visible icterus on admission nor any petechiae or ecchymoses. Neurologic findings were within physiologic limits.

*Laboratory Data*—The results of laboratory examination of the blood have been tabulated as follows:

Blood count	4/23/42	5/19/42
Hemoglobin, Gm/100 cc	17.5	10.8
Red cells	5,000,000	2,660,000
White cells	22,080	
Nucleated red cells/100 white cells	15	
Rh antigen	Present	
Kline reaction	Negative	
Serum protein, mg/100 cc (4/25/42)	5.2	
Icteric index (5/4/42)	150	

*Course of Illness*—Shortly after admission jaundice appeared and steadily increased during the first ten days. On the third day the infant was listless and



*Physical Examination*—The temperature was 37 C (98.6 F), and the pulse rate was 120 per minute. No icterus or edema was apparent seven hours after birth. The cord was moderately icteric. Positive physical findings were a liver palpable 3 cm and a spleen palpable 1 cm below the costal margin. The infant became icteric during the first few days of life.

*Laboratory Data*—A blood count revealed 160 Gm of hemoglobin per hundred cubic centimeters, 4,200,000 red cells, 11,800 white cells and 214 nucleated red cells per hundred white cells. The blood contained Rh antigen and gave a negative Kline reaction.

*Course of Illness*—With repeated transfusions the infant did well except for occasional vomiting. The number of red cells and the hemoglobin level tended to fall at first but were kept up with repeated transfusions. Nucleated red cells disappeared after October 10. The infant was discharged on November 16 and was doing well when last seen.

*Case 5 (fig 5)*—Baby I, American, was hospitalized from October 18 to Nov 16, 1941.

*Familial History*—The mother, aged 29, was living and well and did not have Rh antigen in her blood. The father, aged 30, was living and well and had Rh antigen. One sibling, aged 17 months, was living and well.

*Past History*—Pregnancy had been uneventful. The infant's weight at birth was 3,040 Gm.

*Present Illness*—The vernix caseosa and the amniotic fluid were noted to be yellow at birth. The infant received 1 cc of menadione in oil intramuscularly on admission to the nursery. Icterus was noted in the nursery, examination of a smear of blood and a blood count revealed the condition, and she was transferred to the pediatric service.

*Physical Examination*—Positive physical findings included deep icterus of skin, scleras and umbilical cord. The liver was palpable 2 cm and the spleen 1 cm below the costal margin.

*Laboratory Data*—The results of laboratory examinations of the blood have been tabulated as follows:

Blood count	
Hemoglobin, Gm/100 cc	12.0
Red cells	3,000,000
White cells	28,000
Nucleated red cells/100 white cells	30
Prothrombin	7%
Icteric index (10-20-41)	68
Rh antigen	Present
Kline reaction	Negative

*Course of Illness*—The icterus was maximal on the second day and then faded. Transfusions were given on the first four days. Nucleated red cells were not seen after October 21, and the number of red cells and the hemoglobin content rose to normal levels by the time of discharge on November 16.

*CASE 6 (fig 6)*—Baby FT, Jewish, was hospitalized from January 30 to Feb 18, 1942.

*Familial History*—The mother, aged 30, was living and well. Her blood contained Rh antigen but not hR antigen. In 1939 a full term infant had been delivered by cesarian section for fetal distress, the infant had died at the age of 1 day. Autopsy,

*Autopsy*—The significant observations post mortem included generalized, moderate icterus and kernicterus, hepatomegaly (weight of liver 200 Gm), splenomegaly (weight of spleen 36 Gm), partial atelectasis, hemorrhages in the gastrointestinal tract, lungs, kidneys and adrenals, and pseudomembranous esophagitis.

Microscopic examination of the liver revealed numerous areas of erythrocytic and myelogenic hemopoiesis. The parenchymal cells were moderately well stained with fair preservation of the architecture and occasional deposits of brown pigment. Similar pigment was also observed in some of the Kupffer cells.

The final diagnosis was erythroblastosis foetalis.

spastic with opisthotonos, carpopedal spasm and muscular twitchings. A lumbar puncture revealed xanthochromic spinal fluid loaded with red cells. At the same time the serum calcium level was 8.2 mg per hundred cubic centimeters. Both menadione and calcium chloride were given intramuscularly, and the neurologic signs diminished in severity by the end of a week, but opisthotonos and hypertonicity were still present. On the seventh day of life, the stools became clay colored and the urine gave a positive reaction for bile. This persisted for several days, after which the icterus gradually diminished in intensity. During the first week of his illness the infant received daily blood transfusions. After this they were given only when the fall in the blood count indicated that hemolysis was proceeding. By the third day nucleated red cells had disappeared from the peripheral blood. The recovery was uneventful until the twentieth day, when diarrhea developed with an accompanying fall in the red cell count to 2,660,000. At present he has recovered from this and is only faintly icteric.

**CASE 8 (fig 8)**—Baby C, American, was hospitalized from May 3 to 5, 1942.

**Familial History**—Both the mother and the father were living and well. Rh antigen was present in the father's blood but not in the mother's. The mother's first pregnancy, with a different husband in 1938, had resulted in an inevitable abortion at five months. Her second pregnancy, with the present husband, had been normal, the child was living and well. Her present pregnancy had been uneventful.

**Past History**—Delivery had been normal, the infant's weight at birth was 3,400 Gm.

**Present Illness**—A few hours after birth the infant was noted to be icteric and was transferred to the pediatric ward.

**Physical Examination**—On admission the infant was deeply jaundiced, had a good cry and activity, but showed clonic twitchings of the lower extremities. The reflexes were hyperactive. The spleen was palpable 2 cm below the costal margin. The liver was not felt. The results of the remainder of the examination were irrelevant.

**Laboratory Data**—The results of the laboratory examination of the blood have been tabulated as follows:

Blood count	5/4/42	5/5/42
Hemoglobin, Gm/100 cc	14.5	11.0
Red cells	2,700,000	2,350,000
White cells	15,500	
Nucleated red cells/100 white cells	7	18
Rh antigen	Present	
Kline reaction	Negative	
Serum protein, mg/100 cc	5.0	
Prothrombin	< 2%	

**Course of Illness**—On admission a transfusion of citrated bank blood was given, along with intramuscular injections of liver extract and menadione in oil (2 cc). The blood count rose temporarily after the transfusion but then fell, and the jaundice deepened. On the morning of the third day the infant suddenly became drowsy, spastic and cyanotic and seemed to be on the verge of respiratory failure. Another transfusion and an infusion of solution of sodium chloride were given, in addition to stimulants and oxygen, but the patient's condition grew worse and he died late that afternoon, after vomiting some blood-tinged matter.

phone when the lever is moved up and down" Lister's<sup>8</sup> case is the first one to be reported in which the sounds appeared spontaneously while the patient was at rest Wolferth and Wood<sup>9</sup> observed a young man who had a spontaneous pneumothorax and who apparently had had a "pericardial knock" In this instance the patient stated that a wrestling match had preceded the onset of precordial pain Fisher<sup>10</sup> and Biering<sup>11</sup> have described what they term spontaneous interstitial and mediastinal emphysema in a newborn infant, but this has always been secondary to congenital atelectasis

Hamman<sup>12</sup> in 1934 described 3 spontaneous occurrences of this condition under the heading of interstitial emphysema and discussed the differential diagnosis from coronary closure In 1937 Hamman<sup>13</sup> reported 4 additional spontaneous occurrences of the syndrome In this paper he included 2 of his previously reported cases, omitting the one in which symptoms occurred after an operation on a paranasal sinus Hamman<sup>14</sup> added another case to his series in 1939 McGuire and Bean<sup>1</sup> gave a comprehensive review of the 8 cases of spontaneous mediastinal emphysema that had been reported previously and added 2 of their own They noted that in 1 of their cases the emphysema had its onset fifteen minutes after a difficult labor and therefore could not be classified as occurring spontaneously In the other case that they reported the patient was a 17 year old girl, and the onset occurred when she was dribbling a basketball in a gymnasium Consideration of this case as one of spontaneous mediastinal emphysema might be questioned inasmuch as it occurred during exertion McGuire and Bean were the first to suggest that this entity be designated "Hamman's disease"

Morey and Sosman<sup>15</sup> in 1939 added another case to this small series By roentgen study they were able to demonstrate the presence of a small

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8 Lister, W A A Case of Pericardial Knock Associated with Spontaneous Pneumothorax, *Lancet* **1** 1225-1226 (June 16) 1928

9 Wolferth, C C, and Wood, F C Angina Pectoris, *M Clin North America* **13** 947-967 (Jan) 1930

10 Fisher, J H Spontaneous Pulmonic Interstitial and Mediastinal Emphysema in an Infant, *Canad M A J* **44** 27-29 (Jan) 1941

11 Biering, A Pneumothorax in Newborn Case of Pneumothorax with Congenital Atelectasis and Mediastinal Emphysema, and Some Remarks on Pathogenesis, with Special Reference to Importance of Congenital Atelectasis, *Acta paediat* **28** 367-384, 1941

12 Hamman, L Remarks on the Diagnosis of Coronary Occlusion, *Ann Int Med* **8** 417-431 (Oct) 1934

13 Hamman, L Spontaneous Interstitial Emphysema of the Lungs, *Tr A Am Physicians* **52** 311-319, 1937

14 Hamman, L Spontaneous Mediastinal Emphysema, *Bull Johns Hopkins Hosp* **64** 1-21 (Jan) 1939

15 Morey, J B, and Sosman, M C Spontaneous Mediastinal Emphysema, *Radiology* **32** 19-22 (Jan) 1939

# SPONTANEOUS MEDIASTINAL EMPHYSEMA

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Mediastinal emphysema following stab wounds or other trauma of the chest has long been recognized. It has also been described as occurring secondary to violent coughing, bronchial asthma, artificial pneumothorax, pneumonia, difficult labor, straining at stool and other forms of extreme effort. McGuire and Bean<sup>1</sup> point out that Laennec<sup>2</sup> described grating sounds and bubbling rales during respiration as diagnostic of subpleural and interlobar emphysema. Skoda<sup>3</sup> subsequently confirmed these signs, and von Rokitsansky<sup>4</sup> described the pathologic aspects of the condition. Muller<sup>5</sup> noted the presence of bubbling crepitations that occurred with the heart beat and the occasional disappearance of cardiac dulness. He observed that the presence of subcutaneous emphysema aided in making the diagnosis of mediastinal emphysema.

Rees and Hughes<sup>6</sup> in a report on wounds of the chest encountered during World War I noted loud "tapping" sounds over the cardiac area in 9 cases of wounds of the left side of the chest. They observed that the sound continued even when the breath was held, although it was louder during inspiration, the sound was synchronous with the heart beat. In some cases, the examiner could hear the noise several paces from the chest and patients at times were also aware of the sounds. Smith<sup>7</sup> subsequently applied the term pericardial knock to this sound, comparing it to a "noise which may be heard in the ear-piece of a tele-

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1 McGuire, J, and Bean, W B. Spontaneous Interstitial Emphysema of the Lungs, *Am J M Sc* **197** 502-509 (April) 1939

2 Laennec, R. *Traite de l'auscultation mediate*, ed 3, Paris, J S Chaude, 1831, vol 1, p 329, cited by McGuire and Bean<sup>1</sup>

3 Skoda, J. *Abhandlung uber Percussion und Auscultation*, ed 4, Vienna, L W Seidel, 1850, p 276, cited by McGuire and Bean<sup>1</sup>

4 von Rokitsansky, K. *Lehrbuch der pathologischen Anatomie*, ed 3, Vienna, Wilhelm Brausmuller, 1856, vol 2, p 12, cited by McGuire and Bean<sup>1</sup>

5 Muller, F. *Ueber Emphysem des Mediastinum*, *Berl klin Wchnschr* **25** 205-208, 1888, cited by McGuire and Bean<sup>1</sup>

6 Rees, W A, and Hughes, G S. Wounds of the Chest as Seen at an Advanced Operating Center, *Lancet* **1** 55-59 (Jan 12) 1918

7 Smith, S M S. Pericardial Knock, *Brit M J* **1** 78 (Jan 19) 1918

the axilla finer crackling sounds were audible. These "boiler-like" sounds might be compared to the noise that one hears on crumpling a handful of cellophane close to the ear and could be heard distinctly several feet from the patient's chest. The rest of the chest was clear. The heart was not enlarged, and it was not displaced either to the right or to the left. There was a normal sinus rhythm, and no murmurs were heard. At the time of this examination there was no correlation noted between the heart beat and the sounds in the chest. The remaining results of physical examination were entirely irrelevant.

An hour after admission, examination of the chest showed a marked decrease in the intensity of the "boiler-like" sounds but many coarse crackling noises were still heard over the same distribution and these seemed to be associated with the heart beat. Two hours after admission, the "boiler-like" sounds had disappeared completely and only a few crackles remained. By the following morning, eighteen hours after admission, all that could be heard were a few crackling sounds over the precordium appearing only during diastole and heard best with the patient lying on his left side. The patient felt fine and because he had not had any pain or discomfort since the previous evening insisted on going home.

A roentgenogram of the chest taken at the time of admission showed a small pneumothorax at the apex of the left lung. Other roentgenograms were taken in an effort to discover air in the mediastinum, but none could be made out. Because of the patient's short stay in the hospital, the laboratory examination was limited. His hemoglobin concentration was 90 per cent (Sahli), and the white cell count was 19,500, with 93 per cent polymorphonuclears and 7 per cent lymphocytes.

#### MECHANISM

Macklin<sup>20</sup> has investigated extensively the mechanism of spontaneous mediastinal emphysema. From experimental work on cats he has been able to demonstrate that with increased intrapulmonary pressure there is a distention of alveoli. With this distention of alveoli there occur many small ruptures in their floors, which overlie the small branches of the pulmonary blood vessels. As the pressure continues, air is forced onward through artificial tunnels in the vascular sheaths toward the root of the lung and may break through into the mediastinum, distending the tissues with large blebs. From this location the air may be forced upward into the root of the neck, the face, the axilla or the wall of the chest, or it may go forward between the parietal pleura and the pericardium. At times the air in the perivascular sheaths may extend into adjoining connective tissue and dissect a path toward the pleura, where a bleb may form under the pleura, this bleb can rupture and produce a pneumothorax. Hamman<sup>14</sup> stated that in man the alveoli may rupture, even though they show no gross evidence of disease. In view of this observation of Hamman, it may be assumed that it is possible for the alveoli to rupture in the absence of recognizable increased intrapulmonary pressure.

<sup>20</sup> Macklin, C. C. Transport of Air Along Sheaths of Pulmonic Blood Vessels from Alveoli to Mediastinum. Clinical Implications, *Arch Int Med* 64: 913-926 (Nov.) 1939.

pneumothorax In 1941, 1 case of spontaneous mediastinal emphysema was reported by Matthews,<sup>16</sup> Pinckney<sup>17</sup> reported 2 cases and Caldwell<sup>18</sup> and Styron<sup>19</sup> reported 1 case each If one omits the case reported by Wolferth and Wood<sup>9</sup> and the 2 cases reported by McGuire and Bean<sup>1</sup> because of the relation to effort, there are on record only 13 instances of this syndrome occurring spontaneously It is of some significance that 5 of them were reported in the past year Because of the ease with which the diagnosis is made and because of the importance of differentiating spontaneous mediastinal emphysema from various vascular accidents, it is deemed advisable to call attention again to this interesting syndrome and to add another case to the small group that has been reported

#### REPORT OF A CASE

S T, a 22 year old automobile mechanic, was admitted to Bellevue Hospital, Feb 21, 1941, complaining of severe pain of one hour's duration in the chest on the left side At the time the pain appeared he was sitting quietly in a chair reading a newspaper, and he stated that he had not done any strenuous work during that day The pain was sharp and knifelike with a maximum intensity over the lower anterior portion of the chest on the left side from where it radiated straight through to the back The pain was made worse by inspiration, and the patient had become somewhat short of breath He was brought to the hospital by car and when seen in the admitting office he stated that he heard noises in his chest which "sounded as if gears were grinding together" His familial history and his past history, including history of previous respiratory and cardiac disorders, were entirely irrelevant

On admission his temperature was 99.4 F, respiration 18 per minute, pulse rate 90 per minute and blood pressure 130 systolic and 82 diastolic He was well developed and well nourished and was not in any acute distress unless asked to inspire deeply There was no dyspnea, orthopnea or cyanosis The skin was warm and of good turgor There were no abnormalities of the head, eyes, ears, nose or throat The trachea was in the midline No emphysema was noted in the tissues of the neck, but there was a definite area of subcutaneous emphysema over the lower portion of the anterior wall of the chest on the left side The expansion of the thorax was good and equal On placing the hand over the anterior aspect of the lower ribs on the left side during deep inspiration it felt as if two surfaces were being rubbed together and then pulled apart The right hemithorax was clear to percussion and auscultation On the left side the chest was resonant throughout, but the percussion note over the precordium seemed somewhat more resonant than usual Anteriorly from the left costal margin to the third rib "boiler-like" sounds of loud intensity were heard, extending into

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16 Matthews, E Spontaneous Mediastinal Emphysema, New Orleans M & S J **93** 523-524 (April) 1941

17 Pinckney, M M Mediastinal Emphysema and Idiopathic Spontaneous Pneumothorax, Virginia M Monthly **68** 315-319 (June) 1941

18 Caldwell, H W Spontaneous Mediastinal Emphysema, J A M A **116** 301-302 (Jan 25) 1941

19 Styron, C W Spontaneous Mediastinal Emphysema, New England J Med **225** 908-909 (Dec 4) 1941

## SUMMARY

In this report I have added another instance of spontaneous mediastinal emphysema to the 13<sup>22</sup> previously reported cases. Half of these cases have been observed by Hamman, and his description of this syndrome is classic. He has emphasized the sudden onset of spontaneous mediastinal emphysema and the significance of the crunching sound heard over the left side of the chest. The experimental work of Macklin has been an outstanding contribution toward the understanding of the mechanism and the pathology of this condition. It is important to differentiate spontaneous mediastinal emphysema particularly from coronary disease, but the picture may also be confused with that of pericarditis, ruptured or dissecting aneurysm and pulmonary embolus. The reporting of 5 cases of spontaneous mediastinal emphysema in the past year indicates that physicians are becoming aware of this picture and are prepared to recognize it. The diagnosis of spontaneous mediastinal emphysema is particularly important in preventing an unnecessarily prolonged convalescence and in saving a patient from unneeded precautions. Undoubtedly, as physicians become more cognizant of this syndrome the diagnosis will be made more frequently.

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22 Since this paper was written, reports of 8 additional cases of spontaneous mediastinal emphysema have appeared, making a total of 22, including the case reported here. These additional reports are as follows: Griffin, R. J. A Diagnostic Sign of Interstitial Emphysema of the Mediastinum, *Ann Int Med* **17** 295-297 (Aug.) 1942; Spontaneous Pneumothorax, Kentucky M. J. **39** 284-288 (Aug.) 1941; Wolfe, B. P. Spontaneous Interstitial Emphysema of the Lungs, *Ann Int Med* **13** 1250-1252 (Jan.) 1940; Murphy, J. P., and Zeis, L. B. Spontaneous Interstitial Mediastinal Emphysema, *J. Missouri M. A.* **39** 5-7 (Jan.) 1942; Miller, J. Spontaneous Interstitial Emphysema of the Lungs, *Ohio State M. J.* **37** 1056-1059 (Nov.) 1941.



## CLINICAL FEATURES

The distinctive sign of mediastinal emphysema is the crunching sound that is heard over the heart with each contraction. This noise has been explained as being produced by the compression of the air-filled mediastinal tissues which lie between the heart and the anterior wall of the chest. As has been stated, one can almost duplicate this sound by crumpling a handful of cellophane close to the ear. To one who is not aware of the possibility of this condition, the nature of the onset may cause him to think of coronary occlusion, pericarditis, ruptured or dissecting aneurysm or pulmonary embolus. Only by a knowledge of the clinical picture of spontaneous mediastinal emphysema will the patient be spared an unnecessarily prolonged convalescent period and a grave prognosis. The onset is sudden and terrifying to the patient. The pain may last a few hours or several days.

The reports of Hamman<sup>21</sup> have done much to bring this syndrome to the attention of members of the medical profession. The large number of cases of spontaneous mediastinal emphysema encountered by him and the careful reporting of his observations have constituted a noteworthy contribution. The following summary of important symptoms is taken from his most recent paper<sup>14</sup> on the subject.

1 Interstitial emphysema of the lung may occur without the least effort, when the patient is quietly standing, sitting or lying down.

2 When the air reaches the mediastinum, distending the mediastinal tissues, the patient complains of pain which is often very severe. Usually the pain is located beneath the sternum, sometimes it radiates to the back [or] neck [or] shoulders, rarely to the arms.

3 There are no constitutional symptoms, no evidence of shock. The temperature, the pulse and respiratory rates, the blood pressure, the leucocyte count are very little if any altered. [Other authors have reported an increased leucocyte count, such as occurred in my patient.]

4 In many instances a peculiar and distinctive sound is heard over the heart synchronous with its contractions. Usually the sound is heard only during systole but at times it may be heard also during diastole.

5 The area of cardiac dullness may be diminished or completely obliterated, the dullness being replaced by a hyperresonant percussion note.

6 Pneumothorax often occurs. The pneumothorax is usually small and may [be detected only by roentgen examination].

7 The roentgenogram is a valuable aid in establishing the diagnosis [particularly in the absence of characteristic sounds over the heart. The detection by a roentgenogram] of air in the mediastinum may be decisive.

8 When air appears in the subcutaneous tissues of the neck the diagnosis is at once assured.

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21 Hamman (footnotes 12, 13 and 14)

and Collip and co-workers<sup>3</sup> have claimed that this concept also applies to the secretion of the anterior lobe. However, since it has been possible more recently to separate not only the piessor and the oxytocic principle from extracts of the posterior lobe but certain individual factors from extracts of the anterior lobe by mild, nonchemical procedures, such as fractional adsorption and electrophoresis, doubt has been cast on the claim that these individual principles represent artificial cleavage products. Heller<sup>4</sup> has suggested that the pituitary principles may not be secreted singly but in groups. Clinical evidence likewise suggests this mode of secretion.<sup>5</sup> Tumors of any secreting cells of the anterior lobe are associated with symptoms which suggest an abnormal secretion of constant groups of factors.

In spite of all this evidence, the question of whether the various types of pituitary cells are capable of secreting each factor singly or their secretion consists of large molecules having multiple activity, the action of which depends on the response of the effector tissue, still awaits final solution. Isolation of the individual factors in pure chemical form plus more accurate demonstration that they exist in the pituitary gland and in the body fluids in significantly different amounts will soon be accomplished, it is hoped.

### THE ANTERIOR LOBE OF THE PITUITARY GLAND

Sevringhaus<sup>6</sup> has stated

Among the disturbances of the several functions of the anterior lobe of the pituitary, only two are susceptible to treatment with any assurance of success at present. These are dysfunctions in the supply of the growth-promoting and gonadotropic factors.

Many physicians doubt whether even these two disturbances can be treated with any assurance of success. However, since these two factors have received most attention from investigators in the field of pituitary function, we shall consider them first.

### THE GROWTH HORMONE OF THE ANTERIOR LOBE

*Experimental Aspects*—Just as normal growth is dependent on a multiplicity of extrinsic factors, so also is it influenced by many intrinsic factors, more than one of the glands of internal secretion

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<sup>3</sup> Collip, J. B., and others. Symposium: The Anterior Pituitary Gland and Its Neuro-Endocrine Relationships, *Tr. Am. Neurol. A.* **61** 7-17, 1935.

<sup>4</sup> Heller, H. Multiplicity of Pituitary Hormones, *Nature*, London **147** 178 (Feb. 8) 1941.

<sup>5</sup> Cameron, cited by Heller<sup>4</sup>.

<sup>6</sup> Sevringhaus, E. L. Dysfunctions of the Anterior Lobe of the Pituitary and Their Treatment, *J. A. M. A.* **116** 221-225 (Jan. 18) 1941.

# Progress in Internal Medicine

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## REVIEW OF THE LITERATURE ON THE PITUITARY GLAND (1940 AND 1941)

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In recent years extensive experimental studies have been carried out in an attempt to delimit the functions of the pituitary body. A bewildering array of data has been accumulated, this tiny gland has been reported to be intimately related to many of the phases of body metabolism and to nearly every other endocrine gland in the body. An attempt to review fully each of the many phases of investigation which have been carried out would result only in confusion, both for the reader and for the reviewers. Consequently, we shall mention only the recent work on the more clearly established functions of the pituitary gland which may be of clinical significance.

The large number of separate hormones postulated as being elaborated by the pituitary, particularly its anterior lobe, has for some time aroused skepticism among the investigators in this field. Indeed, it does seem almost incredible that an organ the size of the pituitary gland, which has in its anterior lobe only two and in its posterior lobe only one type of acknowledged secretory cell, should elaborate so many different substances. Some investigators, therefore, have suggested that several or even all of the presumably individual hormones might represent cleavage products of larger molecular compounds, that is, artefacts produced by the physical and chemical procedures employed in their isolation. Abel and associates<sup>1</sup> first made this suggestion in connection with the secretion of the posterior lobe. Riddle<sup>2</sup>

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1 Abel, J J, Rouiller, C A, and Geiling, E M K. Further Investigations on the Oxytocic-Pressor-Diuretic Principle of the Infundibular Portion of the Pituitary Gland. II. A Preliminary Therapeutic Study of the Active Principle of the Infundibular Portion of the Pituitary Gland in Four Cases of Diabetes Insipidus, *J Pharmacol & Exper Therap* **22** 289-328 (Nov) 1923

2 Riddle, cited by Heller<sup>4</sup>

of the anterior lobe. On the other hand, Marks and Young<sup>11</sup> claimed that although insulin-increasing (pancreatotropic) substance accompanied the growth-promoting factor in extracts of anterior pituitary, the two factors were not identical.

Ingalls and Hayes<sup>12</sup> attributed to the adrenal cortex the same role in growth as Mirsky assigned to the pancreas. They stated that atrophy of the adrenal glands, which has been shown to occur after hypophysectomy, may be the major factor in the interruption of growth which ensues, a marked failure of endochondrial bone formation, similar to that which follows hypophysectomy, was demonstrated after ablation of the adrenal glands.

Shipley and Long<sup>13</sup> felt that the ketogenic, diabetogenic and growth-promoting hormones might be identical. Greaves and his associates<sup>14</sup> recently suggested that not only the ketogenic but the respiratory quotient-reducing factors were related to the growth hormone.

*Clinical Aspects*—Reviews of the clinical syndromes presumably due to disturbances of the growth factor have been presented by Sevringhaus<sup>6</sup> and Wohl<sup>15</sup>. Briefly, these dysfunctions were classified by these authors as follows:

**Gigantism** This condition presumably is due to excessive activity of the anterior lobe in stimulating growth during childhood and early adolescence. As Sevringhaus has pointed out, irradiation of the pituitary gland in children with this condition with the view to reducing the stimulation to body growth is not to be recommended because of the possibility of interfering with other functions of the pituitary. In any event, an attempt to limit stature should not be made before the child has reached a height of at least 5 feet (152 cm), since the excessive rate of growth may cease spontaneously at about that time. Epiphyseal union which is delayed may be hastened by the administration of thyroid, estrogen or androgen. Many physicians, however, do not believe in any treatment for persons whose height is within reasonably normal limits.

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11 Marks, H. P., and Young, F. G. Hypophysis and Pancreatic Insulin, *Lancet* **1** 493-497 (March 16) 1940.

12 Ingalls, T. H., and Hayes, D. R. Epiphyseal Growth. Effect of Removal of Adrenal and Pituitary Glands on Epiphyses of Growing Rats, *Endocrinology* **29** 720-724 (Nov.) 1941.

13 Shipley, R. A., and Long, C. N. H. Studies on Ketogenic Activity of the Anterior Pituitary. I. Relation of Ketonaemia to Ketonuria in the Rat, II. A Method for the Assay of Ketogenic Activity, III. The Nature of the Ketogenic Principle, *Biochem. J.* **32** 2242-2256 (Dec.) 1938.

14 Greaves, J. D., Freiberg, I. K., and Johns, H. E. Preparation and Assay of Anterior Pituitary Fractions Rich in Ketogenic and Respiratory Quotient-Reducing Substances, *J. Biol. Chem.* **133** 242-259 (March) 1940.

15 Wohl, M. G. Diagnosis and Treatment of Anterior Pituitary Disturbances, *West J. Surg.* **49** 309-317 (June) 1941.

have been shown to have definite relations to growth. Consequently, the claim that the pituitary gland elaborates a hormone essential for growth has only gradually gained validation. There is still some question as to whether the pituitary gland regulates growth through the direct action of a "growth hormone" or through an effect on one or more of the other endocrine glands, the target organs, known to be influenced by the hypophysis. The bulk of the evidence obtained to date seems to indicate that growth-stimulating extracts of the anterior lobe of the pituitary gland do not obtain their result by virtue of their content of the four well known principles affecting target organs (thyrotropic, lactogenic, adienotropic and gonadotropic principles<sup>6</sup>). Reinhardt and his co-workers<sup>7</sup> have reported that the thymus likewise is not a target organ through which the effect of the growth principle is mediated. Evans<sup>8</sup> has made the definite statement that the growth factor is "clearly separate from the target organ hormones". He doubts, however, that "an equally decisive answer" can be given as to whether

the promotion of growth by anterior pituitary extracts is due to one or more of the incompletely separated metabolic "hormones" of the anterior lobe, i. e., the ketogenic, glycotropic, glycostatic, contrainsular, diabetogenic, pancreatropic, nitrogen-retaining and other factors.

The exact mode of action of the growth principle is still unknown. Greene and Johnston<sup>9</sup> reported that balance studies of nitrogen, sulfur, calcium and phosphorus made on 3 typical primary pituitary dwarfs and on 3 nonpituitary dwarfs both before and after the administration of growth-promoting extracts of the anterior lobe showed that the immediate effect was to decrease storage of these elements and the later effect was to increase their storage. Mirsky<sup>10</sup> suggested that extracts of the anterior lobe had two effects on protein metabolism, a direct one on protein catabolism in the muscles and an indirect one, mediated through the pancreas, stimulating protein anabolism. Thus, the stimulation of growth depended on the pancreatropic action of the extracts.

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7 Reinhardt, W. O., Marx, W., and Evans, H. M. Effect of Pituitary Growth Hormone on the Thymectomized Rat, *Proc. Soc. Exper. Biol. & Med.* **46** 411-415 (March) 1941.

8 Evans, H. M. Growth Hormone of the Anterior Lobe of the Pituitary Gland, *J. A. M. A.* **117** 287-291 (July 26) 1941.

9 Greene, J. A., and Johnston, G. W. Pituitary Dwarfism: Metabolic Changes by Extracts of Anterior Hypophysis in Primary-Pituitary and in Non-pituitary Dwarfs, *J. Clin. Endocrinol.* **1** 327-330 (April) 1941.

10 Mirsky, I. A. The Influence of the Anterior Pituitary Gland on Protein Metabolism, *Endocrinology* **25** 52-56 (July) 1939.

**Failure of the Anterior Lobe to Secrete the Growth Principle in Adult Life** Such failure has not been associated with any definite syndrome. The condition known as pituitary cachexia, or Simmonds' disease, usually is assumed to be the result of complete destruction or degeneration of the anterior lobe with failure of all of its functions. We shall discuss this condition in greater detail under a separate heading.

*Summary*—In summary, then, we may say that experimental evidence points to a role of primary importance for the anterior lobe of the pituitary in normal growth mechanisms, but it is not established definitely as yet whether a single growth hormone or several factors which influence target organs are concerned. The clinical value of growth-promoting extracts of the anterior lobe of the pituitary gland is even more indefinite, and wide acceptance of these preparations as therapeutic agents of proved activity awaits the presentation of much more evidence than is now at hand.

#### THE GONADOTROPIC HORMONES OF THE ANTERIOR LOBE

In our discussion of gonadotropins we shall confine ourselves to a consideration of those which are obtained directly from the pituitary gland and those which are presumably of pituitary origin, extracted from the blood and the urine of normal men and women and of women who have undergone the menopause. Those gonadotropins which are found in the body fluids in the presence of living chorionic tissue (during pregnancy) originate from the chorionic cells and not from the anterior lobe of the pituitary gland and do not belong in our discussion. However, it should be noted that these chorionic gonadotropins have been shown to be much more active physiologically than are the available preparations of pituitary gonadotropins. Consequently, they offer much more hope of extensive therapeutic usefulness than do the pituitary factors.

*Experimental Aspects*—Several gonadotropins have been reported as being elaborated by the anterior lobe of the pituitary gland, but there is no general agreement as to their identity, with the possible exception of the so-called "follicle-stimulating" and "luteinizing" factors. The evidence for the separate entity of these two factors is not completely convincing.

There can be little doubt, however, that the pituitary gland exerts a powerful influence on the gonads in both sexes and that, in turn, the gonads have definite effects on the anterior lobe. Spaying in the young female animal is followed by cytologic changes in the anterior lobe of the pituitary gland, these changes can be reversed by the administration of estrogens. In addition to the cytologic changes the amount of gonadotropin present in the anterior lobe is increased after castration. Furthermore, administration of estrogens to young female rats produces

**Acromegaly** Acromegaly presumably is due to excessive secretion of the growth factor after epiphysial union has taken place. If a tumor of the pituitary gland can be demonstrated and disturbances of the visual field exist, surgical intervention is indicated. In those instances in which a tumor is found but disturbances of vision have not occurred, irradiation of the lesion is often employed. A trial of treatment with estrogens has been recommended by some investigators but has not met with encouraging success. Experimentally at least, estrogens have been shown to inhibit function of the anterior lobe. Not infrequently, the process burns itself out spontaneously.

**Dwarfism** Underactivity of the growth-promoting hormone of the anterior lobe of the pituitary gland during childhood has been claimed to be the cause of certain types of dwarfism characterized by infantilism, failure of the secondary sex characters to develop, low basal metabolic rate and failure of hair growth. Providing other causes for the failure to grow, such as primary hypothyroidism, can be excluded, treatment with aqueous pituitary extracts containing the growth factor may be employed. Growth-promoting preparations at present are generally made from fresh or acetone-desiccated tissue from the anterior lobe of the pituitary. They usually are standardized by measurement of their capacity for producing growth in young hypophysectomized or normal rats. Although purified the best preparations of this sort cannot lay claim to being simple homogeneous substances. Because their action is brief, they must be given daily. Evans<sup>8</sup> did not recommend the administration of crude extracts of the anterior lobe because not only must large quantities be employed but such undesirable consequences as gonadotropic and diabetogenic effects may ensue. Sevringhaus<sup>9</sup> advised against the use of desiccated thyroid with a preparation of the anterior lobe of the pituitary containing the growth principle since the former substance tends to hasten epiphyseal closure.

Despite the difficulties encountered in the treatment of this type of patient a considerable number of such dwarfed children have been reported to have improved with treatment. Most observers, however, have been disappointed with the clinical use of growth principle. More extensive clinical use of this factor awaits the preparation of a purified preparation of the specific growth-promoting principle and more convincing evidence, both experimental and clinical, of its activity. Instances have been reported of acceleration of growth following the administration of "gonadotropic" substances<sup>16</sup>

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<sup>16</sup> Dorff, G. B. Chorionic Gonadotropic Effects on Growth in Sexually Underdeveloped Older Boys, *Am J Dis Child* **60** 1043-1057 (Nov) 1940, Rapid Growth in Height Produced by Chorionic Gonadotropin in a Dwarfed, Infantile Identical Twin, *J Clin Endocrinol* **1** 940-944 (Dec) 1941. Shelton, E. K. The Clinical Aspects of Dwarfing, *Endocrinology* **30** 1000-1014 (June) 1942.

tois<sup>22</sup> have described what they claim to be nearly pure follicle-stimulating substance, which in their experience stimulated follicular growth but did not produce an estrogenic effect, as measured by uterine and vaginal changes

In the hypophysectomized male rat the follicle-stimulating extract produces a reaction analogous to that in the female animal. The epithelium of the seminiferous tubules is maintained or repaired, and formation of sperm appears. However, the interstitial tissue of the testis remains atrophic both histologically and functionally, as evidenced by the atrophic state of the accessory sex glands, the prostate gland and the seminal vesicles.

Proof of the occurrence of the so-called "luteinizing hormone" as a separate entity is particularly hard to obtain when its effect on the ovary of the rodent is studied. Exponents of the dual hormone theory claim that this factor does not have any effect on the ovary of the hypophysectomized female rat, because luteinizing changes can be produced only in follicles which have already ripened to a certain degree. If both the follicle-stimulating and the luteinizing factors are given simultaneously, luteinization and sometimes ovulation results, the ovarian weight increases beyond the sum of the increases produced by the two substances separately, the so-called "augmentation phenomenon." Those who deny the dual hormone theory point out that certain nonspecific substances (zinc sulfate and egg albumin) have been shown<sup>23</sup> to be more effective in the production of this phenomenon when given in combination with follicle-stimulating substance to a female animal than is the luteinizing substance itself.

A more distinct effect is produced in the hypophysectomized male rat by the luteinizing extract. Its administration results in growth and functional activity of the interstitial cells of the testis, as indicated by their histologic appearance, as well as by the growth and development of the accessory sex glands, the prostate gland and the seminal vesicles presumably as a result of secretion of androgen. The nonspecific substances mentioned previously have not been shown to be capable of stimulating the effects of the luteinizing substance on the interstitial cells of the testis in the hypophysectomized male rat.

Greep<sup>24</sup> recently has added some evidence in favor of the two hormone theory. He produced parabiosis of a hypophysectomized imma-

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22 Shedlovsky, T., Rothen, A., Greep, R. O., van Dyke, H. B., and Chow, B. F. The Isolation in Pure Form of the Interstitial Cell-Stimulating (Luteinizing) Hormone of the Anterior Lobe of the Pituitary Gland, *Science* **92** 178-180 (Aug. 23) 1940.

23 Saunders, F. J., and Cole, H. H. On the Reliability of Present Methods for Characterizing Two Gonadotropic Hormones, Follicle-Stimulator and Luteinizer, *Endocrinology* **23** 302-317 (Sept.) 1938.

24 Greep, R. O. Pituitary Function in Parabiotic Triplet Rats, *Proc. Soc. Exper. Biol. & Med.* **44** 214-217 (May) 1940.



luteinization in the ovaries Doisy<sup>17</sup> was of the opinion that this effect may be due to the release of additional luteinizing principle by the anterior lobe

In the male animal both functions of the testis, spermatogenic and endocinous, are induced by, and dependent for maintenance on, the gonadotropins from the anterior lobe of the pituitary<sup>18</sup> In turn, testicular secretions limit the production by the pituitary gland of gonad-stimulating material Moore<sup>19</sup> stated that seasonal testicular activity in animals "seems to be a problem of pituitary activity"

The difficulty in clearly separating the actions of each of the gonadotropins of the anterior lobe is largely the result of having to depend for differentiation on biologic tests, which are complicated by lack of distinct end points Particularly unreliable, in the opinion of Engle and Levin<sup>20</sup> are those results obtained on intact animals in which their own pituitary glands undoubtedly participated in the experiment These authors stated that only the hypophysectomized rat or mouse affords standard test conditions

In the hypophysectomized female rat the purified follicle-stimulating extract produces growth and development of numerous follicles, associated with an increase in ovarian weight Some investigators have claimed that if it is completely separated from the luteinizing factor, the follicle-stimulating principle does not produce any changes of the type ordinarily attributed to the luteinizing factor Others have reported that the best preparations of either factor if injected in sufficiently large doses or over sufficiently long periods will induce the changes usually ascribed to the other Furthermore, by manipulating the rate at which the administered gonadotropin reaches the ovary the reactions ascribed to the luteinizing factor may be made to appear or disappear

The follicle-stimulating factor has been reported to have a secondary effect, namely, the development of the secondary sex characters, presumably because of the secretion of estrogen by the developing follicles However, Greep and his co-workers<sup>21</sup> and Shedlovsky and his collabora-

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17 Doisy, E A The Estrogenic Substances, *J A M A* **116** 501-505 (Feb 8) 1941

18 Hamilton, J B Therapeutics of Testicular Dysfunction, *J A M A* **116** 1903-1908 (April 26) 1941

19 Moore, C R Physiology of the Testis, *J A M A* **116** 1638-1644 (April 12) 1941

20 Engle, E T, and Levin, L Gonadotropine of the Anterior Lobe of the Pituitary and of Chorionic Tissue, *J A M A* **116** 47-52 (Jan 4) 1941

21 Greep, R O, van Dyke, H B, and Chow, B F Separation in Nearly Pure Form of Luteinizing (Interstitial Cell Stimulating) and Follicle-Stimulating (Gametogenic) Hormones of the Pituitary Gland, *J Biol Chem* **133** 289-290 (March) 1940

Determination of the urinary content of gonadotropins of human subjects has received wide attention, probably because dysfunctions of the reproductive organs are among the most common endocrine disturbances encountered and because methods of bioassay for these principles are relatively simple. Despite the fact that numerous reports on analyses of the urine for gonadotropins have appeared in the literature in the past few years, it is only recently that reasonably accurate data on normal subjects have been obtained.

Several years ago Katzman and Doisy<sup>29</sup> found that in children little or no gonadotropic substance was excreted until the period just preceding the onset of puberty, at this period appreciable amounts could be found. Witschi and Riley<sup>30</sup> found in assays of 100 pulverized, acetone-dried, human pituitary glands that those of children contained only small quantities of gonadotropic principle.

Earlier observations on normally menstruating women indicated that excretion of gonadotropin was insignificant except during the period between the twelfth and the sixteenth day of the cycle, this peak of excretion was assumed to coincide with ovulation. More recent data, however, indicate that an increased excretion of gonadotropins could be observed at any point during the menstrual cycle, although a consistent increase in output seemed to precede the establishment of the menstrual flow.<sup>31</sup> D'Amour and associates<sup>32</sup> found several different types of cycle on daily tests for urinary gonadotropins during fifty complete menstrual cycles and concluded that either "ovulation may occur more than once during the menstrual cycle or ovulation is not directly dependent on the amount of gonadotropin in circulation."

Heller<sup>33</sup> has reported the results of assays for urinary gonadotropic substance during twenty-two complete menstrual cycles of 19 normal young women. She found that this substance was excreted at low levels throughout the cycle. Cyclic increases in the amounts excreted occurred in all but 1 case. However, the pattern of periodic increased excretion of gonadotropin in the urine varied greatly not only as to time relations but as to the number and the magnitude of the peaks of excretion.

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29 Katzman, P. A., and Doisy, E. A. A Quantitative Procedure for Determining Normal Excretion of Prolan, *Proc Soc Exper Biol & Med* **30** 1188-1191 (June) 1933.

30 Witschi, E., and Riley, G. M. Quantitative Studies on the Hormones of Human Pituitaries, *Endocrinology* **26** 565-576 (April), 1940.

31 Freed, S. C. Clinical Significance of Hormone Assays, *J A M A* **117** 103-110 (July 12) 1941.

32 D'Amour, F. E., Funk, D., and Liverman, H. Daily Gonadotropic Hormone Tests During Fifty Complete Menstrual Cycles, *Am J Obst & Gynec* **37** 940-946 (June) 1939.

33 Heller, E. J. Gonadotropic Hormone Urine Assays During the Menstrual Cycle in Normal Women, *J Clin Endocrinol* **1** 813-820 (Oct) 1941.

ture male rat and of a hypophysectomized immature female rat with a third rat which had been castrated. Thus a pair of testes and a pair of ovaries were simultaneously subjected to the same gonadotropin in identical dosage. Development of all the testicular elements was noted, whereas only follicular stimulation was found in the ovaries.

Further clarification of the problem of the two gonadotropic hormones awaits the preparation of chemically pure substances, and recent work indicates that we shall not have too long to wait. Data which indicate chemical homogeneity have been reported for at least one preparation of the luteinizing factor by Shedlovsky and associates<sup>22</sup>. Greep and his co-workers<sup>25</sup> have reported the preparation of pure luteinizing principle (metakentrin) and of pure follicle-stimulating principle (thylakentrin). Simpson, Li and Evans<sup>26</sup> have reported on the biologic properties of an interstitial cell-stimulating principle from the pituitary gland. The preparation used was capable of maintaining spermatogenesis and activity of the interstitial cells in the adult hypophysectomized male rat.

*Assay of Urinary Gonadotropins*—Urinary gonadotropins can be assayed only by biologic methods the accuracy of which is dependent on careful control of many factors. Several methods are available<sup>20</sup>. Drips and Osterberg<sup>27</sup> have reported that the Frank method for measuring urinary gonadotropins was useful as an adjunct to clinical diagnosis of ovarian dysfunction. In this method a combination of gross examination, including measuring the weight, of the uterus and the ovaries of the test animals with microscopic examination of the ovaries for evidence of follicle stimulation and luteinization is employed. Gustavson and D'Amour<sup>28</sup> stated that the method which depends for its end point on vaginal cornification in the test animal should be recommended most highly.

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25 Greep, R. O., van Dyke, H. B., and Chow, B. F. Gonadotropins of the Swine Pituitary. I. Various Biological Effects of Purified Thylakentrin (FSH) and Pure Metakentrin (ICSH), *Endocrinology* **30** 635-649 (May) 1942. Chow, B. F., van Dyke, H. B., Greep, R. O., Rothen, A., and Shedlovsky, T. Gonadotropins of the Swine Pituitary. II. Preparation and Biological and Physiochemical Characterization of a Protein Apparently Identical with Metakentrin (ICSH), *ibid* **30** 650-656 (May) 1942. Chow, B. F. Gonadotropins of the Swine Pituitary. III. Immunological Specificity of Swine Metakentrin, *ibid* **30** 657-661 (May) 1942.

26 Simpson, M. E., Li, C. H., and Evans, H. M. Biological Properties of Pituitary Interstitial-Cell-Stimulating Hormone (ICSH), *Endocrinology* **30** 969-976 (June) 1942. Comparison of Methods for Standardization of Pituitary Interstitial-Cell-Stimulating Hormone (ICSH), *ibid* **30** 977-984 (June) 1942.

27 Drips, D. G., and Osterberg, A. E. An Evaluation of the Frank Method for the Determination of Prolan (Gonadotropic Principle) in the Urine of Non-pregnant Women, *Endocrinology* **23** 703-710 (Dec) 1938.

28 Gustavson, R. G., and D'Amour, F. E. The Assay of Gonadotropins and of Gonadal Hormones, *J. A. M. A.* **117** 188-193 (July 19) 1941.

tois have failed to find increased excretion of this principle in aged men with varying degrees of genital involution<sup>36</sup>

On the other hand, Hamilton<sup>18</sup> reported that loss of testicular function leads to increased secretion of gonadotropins by the pituitary gland and that determinations of urinary gonadotropin might serve to indicate whether atrophy or underdevelopment of the testis is primarily referable to testicular hyposecretion or is secondary to lesions in the pituitary gland

*Clinical Aspects*—Sevringhaus has presented a summary of the clinical syndromes associated with dysfunctions in the supply of gonadotropins. Briefly, he outlined them about as follows

**Hyperecretion** The only condition associated with excessive amounts of gonadotropins of the anterior lobe of the pituitary body is the female climacteric. Sevringhaus has stated that there is no evidence indicating that the appearance of increased amounts of gonadotropin in the pituitary gland, blood and urine of women undergoing the menopause "has any significance for the comfort or health of the patient." Complete relief of symptoms with the dose of estrogen usually employed, he stated, is not due to inhibition of the secretion of the anterior lobe, since typically high climacteric levels of gonadotropic substance in the urine may remain after clinical improvement has occurred.

Other investigators, however, have contradicted Sevringhaus' opinion on the relation between the excess secretion of gonadotropins by the pituitary gland and the symptoms of the menopause. Kaplan<sup>37</sup> reported that irradiation of the pituitary gland was an effective means of controlling the symptoms of the menopause. He claimed that under such circumstances "functional hyperplasia" of the cells of the anterior lobe existed and that irradiation reduced their activity. Pendergrass, Hodes and Griffith<sup>38</sup> likewise reported beneficial results from irradiation of the pituitary glands of menopausal patients. These observations await confirmation.

Lawrence and Moulyn<sup>39</sup> reported that the presence of excessive urinary gonadotropin was a good guide to the selection of patients who might be expected to respond favorably to estrogen therapy. Only 48 of 100 patients who came to them because of symptoms of menopause

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36 Leatham, J. H., and Levin, L. Gonadotropic Action of Normal Male Urine Extract on Ovaries of Normal and Hypophysectomized Immature Rats and of Immature Mice, *Endocrinology* **29** 8-17 (July) 1941

37 Kaplan, I. I. Irradiation of Brain Tumors at Bellevue Hospital, 1924-1939, *Radiology* **36** 588-595 (May) 1941

38 Pendergrass, E. P., Hodes, P. J., and Griffith, J. Q. Irradiation of Pituitary Gland in Posterior Lobe Hyperfunction Controlled by Biologic Tests, *Am J Roentgenol* **46** 673-682 (Nov) 1941

39 Lawrence, C. H., and Moulyn, A. C. The Menopause: Hormonic and Therapeutic Study, *New England J Med* **224** 845-847 (May 15) 1941

observed. She concluded that excretion of gonadotropins did not make a distinct pattern which might be classed as normal. Consequently, she was of the opinion that determinations of urinary gonadotropins would not be of any diagnostic value except in the extremes of gonadal dysfunction.

Although the exact nature of the gonadotropin excreted by normal women has not been established as yet, a limited study by D'Amour<sup>34</sup> indicates that this substance is similar to that excreted after the menopause.

The findings in studies on nonpregnant women with amenorrhea have been more conclusive than those in studies on normally menstruating women. It seems well established that the woman with amenorrhea due to spontaneous ovarian failure or to surgical castration excretes an increased quantity of gonadotropin. Salmon and his associates<sup>35</sup> detected an increase in urinary gonadotropin within three days after ovariectomy. These findings coincide with the report of Witschi and Riley<sup>30</sup> that pituitaries from elderly women and castrated persons showed the highest gonadotropic potency among the human glands studied.

In clinical experience tests for urinary gonadotropin in cases of amenorrhea have proved of value in determining whether the ovary or the pituitary is at fault. If the failure to menstruate is due to failure of the pituitary, little or no gonadotropin will be excreted, if it is due to ovarian failure, gonadotropin will occur in the urine in most instances and in many cases the amount will be increased.

Witschi and Riley reported that during the first period of pregnancy the pituitary rapidly lost its gonadotropic potency, it regained it slowly toward the end of pregnancy and rapidly in the puerperium.

These same authors have reported that in the reproductive age groups the hypophyses of men contained four times more gonadotropic principle than did the glands of nonpregnant women. This report coincides with other reports in the literature which indicate that normal men excrete somewhat larger amounts of gonadotropin than do normal women. However, the excretion in men does not appear to be cyclic. Studies of the nature of this urinary gonadotropin of normal men indicate that it is similar to, or identical with, that excreted by ovariectomized or menopausal women. Although increased amounts of gonadotropin have been shown to be excreted by postclimacteric women, several investiga-

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34 D'Amour, F. E. Qualitative Study of Normal Gonadotropins, *Am J Physiol* **127** 649-653 (Nov) 1939.

35 Salmon, U. J., Geist, S. H., and Walter, R. I. Inhibitory Effect of Implanted Estrogenic Hormone Crystals upon Post-Menopause and Castration Hypophysis of Women, *Proc Soc Exper Biol & Med* **43** 424-426 (Feb) 1940.

chidism Infantilism, in which the testes fail to grow, has been treated with gonadotropic substances, with varying degrees of success. In cases of so-called "adiposogenital dystrophy," in which in addition to genital immaturity and infantilism there is marked obesity, a dietary regimen alone or in conjunction with gonadotropic therapy may be tried. In many instances a reduction diet alone will produce satisfactory results. Schwarz, Newman and Baum<sup>42</sup> reported that in patients with this disorder the administration of gonadotropic substances did not have any effect on the obesity, even though they induced genital development. Treatment of cryptorchidism usually involves a combination of glandular therapy with surgical procedures. Thompson and Heckel<sup>43</sup> stated that glandular therapy often enables the physician to determine whether operative procedures will be necessary at an early age in the individual case. In their experience chorionic gonadotropin has proved most satisfactory. If mechanical obstruction does not exist, the testis often will descend with glandular therapy alone. If the testis does not descend because of some obstruction Thompson and Heckel are of the opinion that glandular therapy still serves the useful purpose of enlarging the parts and thus facilitating subsequent surgical procedure. Counseller<sup>44</sup> recommended that surgical treatment be delayed in cases of cryptorchidism until puberty, since in many instances spontaneous descent of the testis will occur at or near that time.

Of the gonadotropic substances available for the treatment of these various "hypogonad states," the chorionic gonadotropin contained in pregnant mare's serum or the gonadotropin in extracts of the anterior lobe of the pituitary, both of which stimulate not only the interstitial but the spermatogenic tissue of the testis, are preferable. Relatively large doses at frequent intervals are desirable.

*Summary*—The close relation of the anterior lobe of the pituitary gland to the gonads of males and of females is acknowledged but not yet clearly understood. Urinary assays for excreted gonadotropins are valuable, particularly in the postclimacteric state, in which an excessive excretion may indicate that a favorable response to estrogen therapy will be obtained. Treatment of hypogonadism of human beings of each sex with gonadotropic substances has been given rather extensive trial. As yet the results which may be anticipated in a given instance cannot be predicted with any degree of accuracy.

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42 Schwarz, H., Newman, A. B., and Baum, H. Pituitary Function in Adiposogenital Dystrophy (Frohlich), *Endocrinology* **26** 605-608 (April) 1940.

43 Thompson, W. O., and Heckel, N. J. Endocrine Treatment of Cryptorchidism, *J. A. M. A.* **117** 1953-1958 (Dec. 6) 1941.

44 Counseller, V. S. Ten Years' Experience in Management of Cryptorchidism, *J. Urol.* **46** 722-731 (Oct.) 1941.

had an excess of urinary gonadotropin, 90 per cent of this group were benefited by the administration of estrogens. Of the remaining 52 patients, who did not have an excess of urinary gonadotropin, only 25 per cent were similarly benefited.

**Hypogonadism in the Female** When evidence of primary ovarian dysfunction or of disturbance of ovarian function by some pathologic process elsewhere in the body is lacking, ovarian hypofunction may be assumed to be the result of failure of the anterior lobe of the pituitary gland to secrete gonadotropic substance. However, exact proof of this relation under such circumstances is not possible because of the present limitations in the accuracy of hormone assay.

A wide variety of clinical types of ovarian hypofunction has been described. This is not surprising when the three functions of the ovary, ovulation, production of estrogen and production of progesterone, are considered. The intensity and duration of disturbances of the last two functions may vary widely. Further variables are the time and the magnitude of secretion by the anterior lobe of the pituitary gland of the two gonadotropic substances, the follicle-stimulating and the luteinizing principle.

Stimulation of the ovaries can be produced by the administration of extracts of the anterior lobe of the pituitary gland and also of concentrates from the serum of pregnant mares. Sevringhaus was of the opinion that the optimal time for a course of treatment with these substances is the first two weeks of the menstrual cycle. Interruption of treatment is advisable, since one investigator at least has reported that continuous ovarian stimulation results in polycystic degeneration of the ovarian tissue.<sup>40</sup>

Ornstein<sup>41</sup> recently reported that in 4 cases of the Lorain-Levi type of hypopituitarism with amenorrhea, neither pregnant mare's serum alone nor in combination with gonadotropin from the anterior lobe of the pituitary gland was effective in inducing menstrual bleeding or in maintaining the secondary sex characters. Cyclic uterine bleeding associated with changes in the secondary sex characters was induced in these cases by the continuous administration of estrogen, in the form of pellets of estradiol benzoate implanted subcutaneously, supplemented by regularly spaced periods during which progesterone was administered by mouth.

**Hypogonadism in the Male** This may occur as one of three fundamental types, namely, infantilism, adiposogenital dystrophy or cryptor-

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40 Buxton, C. L. The Effects of Certain Gonadotropic Extracts on Anovulatory Cycles and Amenorrhea, *Am J Obst & Gynec* **42** 236-241 (Aug) 1941

41 Ornstein, E. A. Management of Primary Amenorrhea in Hypopituitarism, *J Clin Endocrinol* **1** 899-904 (Nov) 1941

the babies were removed from the breast simultaneously with the administration of the hormones. Since the maintenance of lactation depends on the nervous stimulus of sucking, which maintains a high secretion of lactogenic hormone by the pituitary gland,<sup>51</sup> in the nonsuckled breast lactation soon might cease spontaneously without any endocrine treatment. Abarbanel and Goodfriend<sup>52</sup> found in a study of 33 parturient women permitted to nurse their babies during the administration of diethylstilbestrol that doses as high as 1 Gm failed to inhibit the onset of lactation and as high as 50 to 500 mg failed to inhibit established lactation. Abarbanel<sup>53</sup> pointed out that the relief of engorgement of the breast with estrogens and androgens was not synonymous with inhibition of lactation. Painful engorgement of the breast is not due to filling of the breast with milk but to lymphatic and venous stasis. Few investigators agree about the degree of suppression of lactation which can be obtained with estrogen.

Meites and Turner<sup>54</sup> in experiments on rats found that the administration of large doses of diethylstilbestrol and testosterone propionate to lactating mother rats for the first six days post partum did not decrease the lactogen content of the pituitary gland but actually increased it, at the same time the amount of milk in the mammary glands was reduced somewhat. Large doses of diethylstilbestrol did not reduce the lactogen content of the pituitary glands of immature and of mature male guinea pigs, actually it was increased. Lewis and Turner<sup>55</sup> found that diethylstilbestrol increased the lactogen content of the pituitary gland of mature spayed rats (female) 226 per cent and even could initiate lactation. Parturient rats which were not suckled in the first week post partum had 50 per cent less lactogen in their pituitary glands than suckled rats, and their mammary glands were practically devoid of milk.<sup>55</sup> Meites and Turner suggested that suppression of lactation in some animals with estrogens and androgens might be due to a decrease in the secretion of hormones of the anterior lobe of the pituitary gland other than lactogen,

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51 Meites, J., Bergman, A. J., and Turner, C. W. Relation of Size of Litter to A. P. Lactogen Content of Nursing Rabbit, *Proc Soc Exper Biol & Med* **46** 670-671 (April) 1941.

52 Abarbanel, A. R., and Goodfriend, M. J. The Effect of Stilbestrol upon Lactation, *Am J Obst & Gynec* **40** 1037-1046 (Dec) 1940.

53 Abarbanel, A. R. The Effects of Testosterone Propionate, Methyl Testosterone, Anhydro-Oxy-Progesterone and Progesterone upon Lactation in the Nursing Human Being, *Am J Obst & Gynec* **42** 110-116 (July) 1941.

54 Meites, J., and Turner, C. W. Studies Concerning the Mechanism Controlling the Initiation of Lactation at Parturition. II. Why Lactation Is Not Initiated During Pregnancy, *Endocrinology* **30** 719-725 (May) 1942.

55 Lewis, A. A., and Turner, C. W. Effect of Stilbestrol on Lactogenic Content of Pituitary and Mammary Glands of Female Rats, *Proc Soc Exper Biol & Med* **48** 439-443 (Nov) 1941.



## THE LACTOGENIC HORMONE OF THE ANTERIOR LOBE

The mechanism responsible for the control of the initiation of lactation at parturition has long been a mystery. Definite progress was not made in this problem until 1928 and 1929, when Stricker and Grueter<sup>45</sup> announced the discovery of a factor produced by the pituitary (lactogenic principle) which was capable of initiating lactation in animals the mammary glands of which had developed suitably. This work has been amply confirmed. Methods for obtaining the lactogenic principle of the anterior pituitary (lactogen) in relatively pure form have been devised.<sup>46</sup>

Various hypotheses have been advanced to explain the absence of lactation during pregnancy and its initiation after parturition. One which has been widely held is that of Nelson,<sup>47</sup> who suggested that the large amounts of estrogen present during pregnancy suppressed lactation by inhibiting secretion of the lactogenic hormone by the anterior lobe of the pituitary or by direct action on the mammary glands or by both. He and many others have claimed that large doses of estrogen could either diminish or completely suppress lactation in various animals. Meites and Turner,<sup>48</sup> however, expressed doubt that an examination of the literature will support these claims. They pointed out that it has been shown<sup>49</sup> that when large amounts of estrogen are given to lactating rats, a considerable amount of the hormone may be excreted in the milk. Since estrogen is known to have a deleterious effect on growth,<sup>50</sup> conclusions concerning suppression of lactation by estrogens based on decrease of the rate of growth of the young as a criterion of lactation may not be valid. Furthermore, the validity of results obtained by administration of estrogen to human beings may be questioned, since in most of the attempts to inhibit lactation with estrogen and androgen,

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45 Stricker, P., and Grueter, F. Action du lobe anterieur de l'hypophyse sur la montee laiteuse, *Compt rend Soc de biol* **99** 1978-1980 1929, *Recherches experimentales sur les fonctions du lobe anterieur de l'hypophyse. Influence des extraits du lobe anterieur sur l'appareil genital de la lapine et sur la montee laiteuse*, *Presse med* **37** 1268-1271 (Sept 28) 1929.

46 Bergman, A. J., Houchin, O. B., and Turner, C. W. Efficiency of Extraction and Separation of Certain A. P. Hormones, *Endocrinology* **25** 547-553 (Oct) 1939.

47 Nelson, W. O. Endocrine Control of the Mammary Gland, *Physiol Rev* **16** 488-526 (July) 1936.

48 Meites, J., and Turner, C. W. Studies Concerning the Mechanism Controlling the Initiation of Lactation at Parturition. I. Can Estrogen Suppress the Lactogenic Hormone of the Pituitary? *Endocrinology* **30** 711-718 (May) 1942.

49 Walker, S. M., and Stanley, A. J. Effect of Diethylstilbestrol Dipropionate on Mammary Development and Lactation, *Proc Soc Exper Biol & Med* **48** 50-53 (Oct) 1941.

50 Nelson, cited by Meites and Turner<sup>48</sup>. Hartman, C. G., Geschickter, C. F., and Speert, H. Effect of Continuous Estrogen Administration in Very Large Dosage, *Anat Rec (supp)* **79** 31 (March) 1941.

exert important supplementary effects on lactation, especially on the precursors of milk. After lactation has been initiated, as mentioned previously the stimulus of nursing is of prime importance in maintaining lactation, probably through a direct action on the lactogen content of the pituitary.<sup>51</sup>

Low secretion of milk may be due not only to underdevelopment of the breasts but to refractoriness of the pituitary gland to stimulation with estrogen or to insufficient estrogen at the time of parturition.<sup>59</sup> Lactogenic hormone or extracts of the whole pituitary gland have been tried to increase lactation, varying degrees of success have been reported. Diethylstilbestrol has been used in animals to increase production of milk.<sup>49</sup> Moderate amounts of estrogen were found to increase lactation, whereas large doses decreased it.

Meites and Turner suggested that assay of the urine for lactogenic principle might be useful for determining whether low secretion of milk by parturient women was due to failure of secretion of lactogen by the pituitary gland.

*Summary*—The extensive work of Meites and Turner and of other investigators has suggested that the lactogenic hormone of the pituitary gland is the factor concerned in both the initiation of lactation at parturition and its maintenance throughout the nursing period. However, the amount of lactogen secreted by the anterior lobe apparently is dependent both on endocinous and on nervous stimulation. During pregnancy progesterone apparently overrides estrogen in respect to the latter's tendency to stimulate secretion of lactogen, consequently the large amounts of estrogen in circulation fail to induce copious lactation. After parturition the ratio of progesterone to estrogen is altered, so that the latter exerts a dominant effect on the anterior lobe of the pituitary, stimulating secretion of lactogen, which in turn initiates lactation. The results of attempts to stimulate lactation by administration of lactogenic principle are uncertain.

#### THE THYROTROPIC HORMONE OF THE ANTERIOR LOBE

As long ago as 1888<sup>60</sup> it was reported that total thyroidectomy resulted in hypertrophy of the pituitary gland in experimental animals. That this stimulation of the pituitary gland, and particularly of its secretion of the thyroid-stimulating (thyrotropic) hormone, occurs among

59 Meites, J., and Turner, C. W. Studies Concerning the Mechanism Controlling the Initiation of Lactation at Parturition. III. Can Estrogen Content Account for Precipitous Increase in the Lactogen Content of the Pituitary Following Parturition? *Endocrinology* **30** 726-733 (May) 1942.

60 Rogowitsch, N. Die Veränderungen der Hypophyse nach Entfernung der Schilddrüse, *Beitr. z. path. Anat. u. z. allg. Path.* **4** 453-470, 1889.

these hormones might influence the yield of milk through their action on the availability of the precursors of milk in the blood

Meites and Turner <sup>56</sup> explained that copious lactation is not initiated during the latter half of pregnancy in spite of well developed mammary glands because the secretion of lactogenic hormone by the pituitary gland remains at a low level, as low as that in the normal, nonpregnant animal. It is puzzling that during pregnancy when large amounts of estrogen are present in the circulation, the amount of lactogen in the pituitary should not increase as it does after the administration of estrogen. Meites and Turner concluded that some factor must be present during pregnancy which nullifies the stimulating effect of estrogen on the lactogenic hormone. They suggested that this factor is probably progesterone, which is also present in large amounts during gestation. Experimental evidence indicates that if a proper dose ratio is present between the two hormones, progesterone can prevent the normal effects of estrogen.<sup>56</sup> Meites and Turner obtained confirmatory evidence for this hypothesis in experiments on immature female guinea pigs. Progesterone alone had no effect on the lactogen content of the pituitary gland, and estrone (theelin) N N R alone increased this content. Suitable combinations of the two substances either entirely prevented or reduced the increase in lactogenic hormone which could be obtained with estrone alone. The authors stated that during pregnancy lactation does not occur because the progesterone-estrogen ratio was such that the progesterone overrode the lactogen-stimulating effects of estrogen.

Within two to five days after parturition the lactogenic hormone in the pituitary glands of animals has increased 200 to 400 or more per cent according to Schilling and Laqueur.<sup>57</sup> The amount of lactogenic principle encountered in the urine of parturient women may be eight to sixteen times as much as can be demonstrated during pregnancy. Peterson<sup>58</sup> has suggested that the posterior lobe of the pituitary gland may be the factor responsible for the increased secretion of lactogen after parturition. Meites and Turner presented evidence to show that solution of posterior pituitary U S P does not increase the lactogen content of the pituitary glands of animals. They stated that estrogen was the inciting factor at parturition which increased the secretion of lactogen and initiated lactation. Undoubtedly hormones other than lactogen (from the parathyroid glands, pancreas and adrenal glands)

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<sup>56</sup> Meites, J, and Turner, C W. Extraction and Assay of Lactogenic Hormone in Postpartum Urine, *J Clin Endocrinol* **1** 918-923 (Nov.) 1941

<sup>57</sup> Schilling, W, and Laqueur, G L. Thyroid-Ovarian Relations. II. The Effect of Castration and Replacement Therapy on Thyroid, Pituitary, Adrenal and Body Weight in Thyrohyperplastic Albino Rats, *Endocrinology* **29** 103-107 (July) 1941

<sup>58</sup> Peterson, W E, cited by Meites and Turner <sup>59</sup>

hypothyroidism should suggest the diagnosis of hypopituitarism. Confirmatory laboratory evidence of hypopituitarism includes a positive result of the salt deprivation test for adrenocortical insufficiency, increased sensitivity to injected insulin, a negative result of the test for follicle-stimulating substance in the urine, low urinary content of the seventeen ketosteroids indicative in the female of activity of the adrenal cortex, and low level of cholesterol in the blood. Treatment of patients with hypopituitarism with pituitary extracts was of no benefit, but a regimen of injections of pregnant mare's serum combined with added salt in the diet and small doses of desiccated thyroid resulted in considerable improvement.

Wilson<sup>65</sup> reported that a considerable percentage of middle-aged women suffering from neuromuscular pains, somnolence, loss of libido, low blood pressure and moderately low basal metabolic rates with increased level of cholesterol in the blood could be relieved by injections of extracts of the anterior lobe of the pituitary.

Lerman<sup>66</sup> reported that the thyrotropic principle of the anterior lobe was capable of producing thyroid hyperplasia and increased basal metabolic rates in animals, presumably by direct effect on the thyroid cells. Starr and Metcoff<sup>67</sup> claimed that a single subcutaneous injection of a preparation of the anterior lobe of the pituitary gland containing thyrotropic principle (antuitin-T) would result in a significant increase in the mean height of the acinar cells within eight to sixteen hours, the effect persisted at least forty-eight hours after the injection. Belasco and Murlin<sup>68</sup> found that in rats the administration of the thyrotropic factor increased the weight of the thyroid in spite of concomitant loss in body weight. Furthermore, this factor greatly increased the rate of oxygen consumption in the thyroid tissue of old rats. Thyroxin itself, on the contrary, depressed respiration in the thyroid tissues and increased storage of colloid material in the thyroid cells. The authors postulated that this last effect might result in loss of ability of the thyroid tissue to return to activity after cessation of thyroid medication. They suggested that in cases in which the need for thyroid medication was only temporary, intermittent injection of the thyrotropic principle supplemented by doses of desiccated thyroid might be preferable to continuous

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65 Wilson, J. A. A Syndrome Responding to Parenteral Anterior Pituitary Extract, *South Med & Surg* **103** 370-372 (July) 1941.

66 Lerman, J. The Physiology of the Thyroid Gland, *J. A. M. A* **117** 349-359 (Aug. 2) 1941.

67 Starr, P., and Metcoff, J. Rapid Response of Guinea Pig Thyroid to Single Injection of Thyrotropic Hormone, *Proc Soc Exper Biol & Med* **46** 306-308 (Feb.) 1941.

68 Belasco, I. J., and Murlin, J. R. Effect of Thyroxin and Thyrotropic Hormone on Basal Metabolism and Thyroid Tissue Respiration of Rats at Various Ages, *Endocrinology* **28** 145-152 (Feb.) 1941.

human beings is suggested by the work of Means <sup>61</sup>. He found that the amount of thyrotropic principle in the blood and urine was greater in patients with myxedema developing after thyroidectomy than that occurring in the body fluids of normal persons.

A pituitary type of myxedema, however, presumably caused by failure of the pituitary gland to secrete the thyrotropic principle, has been reported by Means, Hertz and Lerman <sup>62</sup> and also by Lerman and Stebbins <sup>63</sup>. In the cases they reported the myxedema-like picture was the predominant feature of primary pituitary cachexia or Simmonds' disease. The clinical findings in these cases so closely resembled those encountered in patients who have primary hypothyroidism that the true diagnosis was unsuspected until acute adrenocortical insufficiency was precipitated by the administration of desiccated thyroid. At necropsy in 1 of these cases the characteristic changes of Simmonds' disease, including atrophy of the pituitary, the thyroid and the adrenal glands and ovaries, were found. Most authors agree that patients who have Addison's disease tolerate thyroid medication poorly although Thompson <sup>64</sup> has stated that correcting low basal metabolic rates in patients with this disease with desiccated thyroid produced clinical improvement of the hypometabolism without aggravating the symptoms of adrenocortical insufficiency. His patients, however, were receiving adequate treatment for their Addison's disease at the time they were given the thyroid medication. In the cases of Simmonds' disease in which symptoms of adrenocortical insufficiency developed during treatment with desiccated thyroid the hypopituitarism had not been recognized previously and hence treatment of the adrenocortical insufficiency had not been given. In 1 case, reported by Lerman and Stebbins, in which this series of complications had developed during thyroid medication, the patient responded well to therapy directed toward the alleviation of the adrenocortical failure.

These same authors pointed out that with the exception of the low basal metabolic rate the signs of hypopituitarism, such as atrophic vaginal mucosa, infantile uterus, loss of libido, amenorrhea, eunuchoid habitus in the male and scanty pubic and axillary hair point to the pituitary as the source of trouble. The finding of hypotension instead of the normal blood pressure or the hypertension ordinarily present in primary

61 Means, J. H. Diseases of the Thyroid Gland, New England J Med **221** 820-825 (Nov. 23) 1939

62 Means, J. H., Hertz, S., and Lerman, J. The Pituitary Type of Myxedema or Simmonds' Disease Masquerading as Myxedema, Tr. A. Am. Physicians **55** 32-53, 1940

63 Lerman, J., and Stebbins, H. D. The Pituitary Type of Myxedema. Further Observations, J. A. M. A. **119** 391-395 (May 30) 1942

64 Thompson, W. O. Addison's Disease. Recent Contributions to Treatment, J. Michigan M. Soc. **39** 648-653 (Sept.) 1940

person, or (2) upset of the integrated control of water balance by the thyroid and the pituitary gland. Perhaps the so-called "ophthalmotropic" principle is normally concerned in the maintenance of water balance.

#### THE ADRENOTROPIC HORMONE OF THE ANTERIOR LOBE

The close relation between the anterior lobe of the pituitary gland and the adrenal cortex has already been mentioned in connection with the "pituitary type of myxedema." In cases of this type atrophy of the adrenal glands with consequent adrenal insufficiency during the life of the patient presumably is caused by failure of the pituitary to secrete an adrenotropic factor.

Stephens<sup>72</sup> reported that in 6 of 7 cases in which clinical evidence of hypopituitarism was found on study with the standard salt deprivation test as outlined by Cutler, Power and Wilder,<sup>73</sup> concentration of chloride in the urine was increased to a degree similar to that which those authors had found characteristic of adrenocortical insufficiency. In 4 of this group of 6 cases symptoms suggestive of acute adrenocortical insufficiency developed during the course of the illness and were relieved promptly by the intravenous administration of salt, dextrose and adrenocortical extract. In 2 cases there was less tendency to excrete an excess of chlorides during the provocative procedure following a regimen of added salt in the diet and injections of adrenocortical extract, in 1 additional case the general clinical appearance of the patient improved considerably on this regimen.

Stephens concluded that the clinical picture of chronic adrenocortical insufficiency frequently accompanied hypopituitarism, he<sup>74</sup> recommended that the salt deprivation test for the former be employed as a precautionary measure prior to the administration of thyroid or surgical procedures in all cases in which pituitary failure is suspected.

In contrast to the hypofunction of the adrenal cortex in hypopituitarism, or Simmonds' disease, is the hyperfunctioning of the adrenal cortex which, according to Albright and his collaborators,<sup>75</sup> is always

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72 Stephens, D. J. Chloride Excretion in Hypopituitarism with Reference to Adrenocortical Function, *Am J M Sc* **199** 67-75 (Jan) 1940.

73 Cutler, H. H., Power, M. H., and Wilder, R. M. Concentrations of Sodium Chloride and Potassium in the Blood Plasma and Urine of Patients with Addison's Disease. Their Diagnostic Significance. *Proc Staff Meet, Mayo Clin* **13** 244-249 (April 20) 1938.

74 Stephens, D. J. Pituitary and Adrenocortical Insufficiency. The Use of Sodium Chloride in the Treatment of Hypopituitarism, *J Clin Endocrinol* **1** 109-112 (Feb) 1941.

75 Albright, F., Pason, W., and Bloomberg, E. Therapy in Cushing's Syndrome. Cushing's Syndrome Interpreted as Hyperadrenocorticism Leading to Hypergluconeogenesis, Results of Treatment with Testosterone Propionate, *J Clin Endocrinol* **1** 375-384 (May) 1941.

thyroid medication alone. Presumably this plan of treatment would facilitate the subsequent resumption of function by the thyroid gland.

Severinghaus, however, stated that in cases of hypothyroidism it was not possible to obtain sustained thyroid stimulation with thyrotropic principle. Consequently, he did not think that irradiation of the pituitary gland was warranted in cases of hyperthyroidism in an attempt to reduce the amount of thyrotropic substance secreted. Chapman<sup>69</sup> recently has reported that the response of the thyroid gland both of intact and of hypophysectomized animals to inadequate intake of iodine was similar. In each instance the thyroid gland responded to the stimulus of low intake of iodine with an increase in weight, an increase in the height of the acinar epithelium and an increase in vascularity. The author concluded from this evidence that the thyroid gland was able to respond to the stimulus of low intake of iodine in the absence of the pituitary gland.

It has been reported on several occasions in the past and recently confirmed by Uotila<sup>70</sup> that thyroid exerted a depressing effect on the thyrotropic function of the anterior lobe of the pituitary. Means<sup>71</sup> reported that the amount of thyrotropic principle demonstrable in the blood and the urine of hyperthyroid patients was less than that found in normal persons.

Friedgood<sup>72</sup> reviewed the theories concerning the mechanism of exophthalmos in cases of parenchymatous hyperplasia of the thyroid gland. He concluded that edema of the orbital tissues was the most likely explanation and that its production was related to the thyrotropic activity of the anterior lobe of the pituitary gland. In experimental animals injections of extracts of the anterior lobe produced an orbital edema which went through two phases, one of which was reversible and the second of which was irreversible. He suggested that the reversible phase was the type ordinarily encountered in exophthalmic goiter. The irreversible phase is encountered rarely in the early stages of exophthalmic goiter and infrequently as a postoperative complication thereof. Friedgood offered two explanations of the cause of the postoperative orbital edema: (1) withdrawal of the normal inhibitor (thyroid secretion) of excessive secretion of the thyrotropic and a separate principle of unknown nature, the exophthalmos-producing (ophthalmotropic) factor, which probably does not exist as such in the pituitary of a normal

69 Chapman, A. The Relation of the Thyroid and the Pituitary Glands to Iodine Metabolism, *Trans Am A Study Goiter*, 1941, pp 169-175.

70 Uotila, U. U. The Regulation of Thyrotropic Function by Thyroxine After Pituitary Stalk Section, *Endocrinology* **26** 129-135 (Jan.) 1940.

71 Friedgood, H. B. Clinical Applications of Studies in Experimentally Induced Exophthalmos of Anterior Pituitary Origin, *J Clin Endocrinol* **1** 804-812 (Oct.) 1941.

Pituitary cachexia usually ends fatally, although it may run a long course. In Escamilla and Lissner's series the course was from thirty to forty years. These authors doubted whether true pituitary cachexia can be benefited materially by any form of therapy, for although "the duration of life may have been prolonged in a few of these patients by glandular therapy, in many of them, it was of no help whatever." However, in 60 per cent of cases in which the clinical picture was typical, although pathologic investigation was not carried out, a variety of endocrine products (pituitary extracts, thyroid, adrenal, ovarian and testicular extracts, insulin, and so forth) produced remarkable improvement. In these cases unintentional psychotherapy, spontaneous resumption of pituitary function or coincidence may have accounted for some of the improvement seen. Indeed, marked improvement in these cases suggests a diagnosis of anorexia nervosa, particularly when the picture is predominantly that of marked loss of weight and low basal metabolic rate in a young unmarried and nulliparous female.

Smith<sup>77</sup> has suggested two diagnostic procedures which may be helpful in the differentiation of anorexia nervosa and pituitary cachexia. He employed a combination of the insulin tolerance test and an assay of the urine for seventeen ketosteroids in making the distinction. In pituitary cachexia a characteristic curve was obtained after injection of insulin, after a normal initial decrease in blood sugar, a failure or a delay in the usual spontaneous return of the blood sugar to normal occurred. Since approximately half of the patients with conditions other than primary pituitary cachexia (such as Addison's disease, severe hepatic disease and severe malnutrition) may have insulin tolerance curves of similar form, assay of the urine for the seventeen ketosteroids is a necessary adjunct to diagnosis. In all but 1 of 10 cases of Simmonds' disease this assay yielded negative results, whereas in cases of other conditions normal or near normal results were obtained.

#### CUSHING'S SYNDROME

Aside from the reports of additional cases of this syndrome, few contributions to the subject have been made in the recent literature.

Albright and his associates<sup>78</sup> claimed that in Cushing's syndrome many of the symptoms and signs were due to hyperglyconeogenesis from body proteins, which produced not only a decreased tolerance for dextrose but a decreased availability of amino acids with which to build protein. They stated that this lack of protein accounted for insulin resistance, mild diabetes, muscular weakness, amenorrhea, impotence, atrophy of the skin and of the walls of the small vessel and osteoporosis.

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<sup>77</sup> Fraser, R., and Smith, P. H. Simmonds's Disease or Panhypopituitarism (Anterior). Its Clinical Diagnosis by the Combined Use of Two Objective Tests, *Quart J Med* **10** 297-330 (Oct.) 1941.



associated with the Cushing syndrome. This syndrome which may be associated with a basophilic adenoma of the pituitary gland or with an adenoma or carcinoma of the adrenal cortex, will be discussed under a separate heading.

No clinical trials of extracts of the anterior lobe of the pituitary gland containing the adrenotropic factor have been reported in the recent literature.

#### SIMMONDS' DISEASE, OR PITUITARY CACHEXIA

Many instances of failure of the pituitary gland, or Simmonds' disease, have been reported, but no general agreement concerning its causation or its treatment has been reached. This diversity of opinion is due partly to the fact that occasionally typical clinical cases may be encountered in which necropsy fails to reveal pathologic changes in the pituitary, the opposite also is found, that is, complete destruction of the pituitary may be discovered at necropsy in a case in which few or none of the phenomena generally associated with pituitary cachexia had been exhibited. Further confusion is added by the fact that Addison's disease rarely and anorexia nervosa frequently simulate closely the clinical appearance of true pituitary cachexia.

Escamilla and Lissner<sup>76</sup> recently published a statistical analysis of 595 cases of Simmonds' disease, in 101 of which the diagnosis was proved by pathologic examination. They included in their paper an excellent review of the literature to date. These authors considered four cardinal symptoms to be necessary for a clinical diagnosis of Simmonds' disease, namely (1) loss of weight, (2) loss of sexual function, (3) asthenia, and (4) a low basal metabolic rate (less than — 20 per cent).

Escamilla and Lissner's study revealed that the disease was more frequently encountered among women than men, during adult life. Of particular etiologic significance they considered (1) infectious processes (in 13 of the 101 pathologically confirmed cases the onset of the disease apparently followed or coincided with an infectious process) and (2) pregnancy (which apparently was of even greater etiologic significance). Pregnancy occurred just before the onset of symptoms in 42 per cent of 67 pathologically verified cases of the disease among women. In more than half of these instances abnormal hemorrhage occurred immediately after parturition. The pituitary is known to undergo rapid involution post partum, presumably, in part at least, because of a reduction in the blood flow to the gland. The authors postulated that if this reduction in blood flow were aggravated by a sudden fall in blood pressure due to hemorrhage, thrombi might be precipitated in the sinuses of the gland and infarction and necrosis might follow.

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<sup>76</sup> Escamilla, R. F., and Lissner, H. Simmonds's Disease. A Clinical Study with Review of the Literature, Differentiation from Anorexia Nervosa by Statistical Analysis of Five Hundred and Ninety-Five Cases One Hundred and One of Which Were Proved Pathologically, *J. Clin. Endocrinol.* 2: 65-96 (Feb.) 1942.

The authors concluded that hypophysectomy resulted in alteration both in the serum albumin and in the serum globulin because of removal of the adienotropic and the thyrotropic hormones, respectively

Sutton<sup>81</sup> reported 6 cases of advanced pellagra in which either great improvement or complete recovery occurred from injections of extracts of anterior pituitary. Stopping the administration of the pituitary extract resulted in relapses. Furthermore, administration of pituitary extracts produced marked clinical improvement in alcoholic polyneuritis and cheilosis even in the absence of an adequate intake of the vitamin B complex. In some cases of achylia in association with pellagra treatment with anterior pituitary extract resulted in a return of gastric secretion. Purified extracts containing the gonadotropic or the growth principle were almost as effective as the whole pituitary extract. In some of the cases of pellagra recovery took place after the patient had failed to respond to therapy with niacin (nicotinic acid), riboflavin, liver administered parenterally and an adequate diet. The author concluded that the hormone or hormones of the anterior lobe of the pituitary gland may be essential to the utilization of the vitamin B complex.

#### RELATION OF THE ANTERIOR LOBE OF THE PITUITARY GLAND TO METABOLISM

*Metabolism of Carbohydrates*—Since the work of Houssay in 1924 the importance of the relation of the anterior lobe of the pituitary gland to carbohydrate metabolism has received much emphasis. Young<sup>82</sup>, Dohan, Fish and Lukens<sup>83</sup>, and Marks and Young,<sup>11</sup> and others have contributed largely to the present knowledge of this subject. Because most of the work on this phase of pituitary physiology has been covered in reviews of metabolism for 1940<sup>84</sup> and 1941,<sup>85</sup> we shall include in this paper mention only of the most recent contributions to the subject.

Houssay and his co-workers<sup>86</sup> recently have reviewed all of the previous work in his laboratory on relations of the anterior lobe of

81 Sutton, D. C. Interrelation Between Vitamin B Complex and the Anterior Lobe of the Pituitary Gland, *South M. J.* **34** 48-51 (Jan.) 1941

82 Young, F. G. Anterior Pituitary Fractions and Carbohydrate Metabolism. I. The Preparation and Properties of Diabetogenic Extracts, *J. Endocrinol.* **1** 339-355 (Nov.) 1939, The Pituitary Gland and Carbohydrate Metabolism, *Endocrinology*, **26** 345-351 (Feb.) 1940

83 Dohan, F. C., Fish, C. A., and Lukens, F. D. W. Induction and Course of Permanent Diabetes Produced by Anterior Pituitary Extract, *Endocrinology* **28** 341-357 (March) 1941

84 Rynearson, E. H., and Hildebrand, A. G. Metabolism and Diabetes. Review of Certain Recent Contributions, *Arch. Int. Med.* **68** 134-175 (July) 1941

85 Hildebrand, A. G., and Rynearson, E. H. Diseases of Metabolism. Review of Certain Recent Contributions, *Arch. Int. Med.* **69** 344-365 (Feb.) 1942

86 Houssay, B. A., Foglia, V. G., Smyth, F. S., Rietti, C. T., and Houssay, A. B. The Hypophysis and Secretion of Insulin, *J. Exper. Med.* **75** 547-566 (May) 1942

Since testosterone propionate has been shown to promote nitrogen storage, Albright treated patients suffering from Cushing's syndrome with this compound. A prompt retention of nitrogen and phosphorus and reestablishment of a positive calcium balance resulted. Associated with the nitrogen retention was a decrease in thinness of the skin, increased muscular strength and loss of easy "bruisability." Treatment of 2 patients with estradiol benzoate did not produce such beneficial results. Progesterone had a slightly favorable effect in 1 instance but generally speaking was inferior to testosterone.

Rakoff and co-workers<sup>78</sup> reported that in 1 case of far advanced Cushing's syndrome treatment with diethylstilbestrol produced clinical improvement within a short time. The blood pressure and the amount of androgens excreted were reduced, however, a preexisting glycosuria was aggravated. In a second case in which the disease was less severe, the improvement under diethylstilbestrol therapy was progressive over a period of one year, during which the patient was under observation. The menses were resumed, and a reduction in body weight and a marked lessening of hirsutism occurred.

#### MISCELLANEOUS FACTORS OF THE ANTERIOR LOBE

In addition to the hormones of the anterior lobe of the pituitary gland which we have discussed in detail, several other factors have been reported in the literature. Since work on these principles is still in the experimental phase and their clinical relations have not become established we shall mention only a few of them briefly.

No recent reports have appeared in the literature concerning the status of the parathyrotropic principle which several years ago was reported to be present in the urine of patients with hyperplasia of the parathyroid glands.

Houchin and Turner<sup>79</sup> reported that in experimental animals the injection of certain extracts of the anterior lobe resulted in a marked rise in the secretion of bile which persisted over a period of four to eight hours.

Levin and Leatham<sup>80</sup> found that hypophysectomy in rats resulted in a fall in serum albumin and a rise in serum globulin. These changes were reproduced to only a slight degree by simple infusion of similar intensity and duration. Administration of thyroid prevented the increase in serum globulin, while administration of adrenal cortical extract or desoxycorticosterone acetate prevented the decrease in serum albumin.

78 Rakoff, A. E., Cantarow, A., and Paschkis, K. E. Cushing's Syndrome. Two Cases Treated with Stilbestrol, *J. Clin. Endocrinol.* **1**: 912-915 (Nov.) 1941.

79 Houchin, O. B., and Turner, C. W. The Relation of the Anterior Pituitary to Bile Production, *Endocrinology* **26**: 821-823 (May) 1940.

80 Levin, L., and Leatham, J. H. The Relation of the Pituitary, Thyroid and Adrenal Glands to the Maintenance of Normal Serum Albumin and Globulin Levels, *Am. J. Physiol.* **136**: 306-313 (April) 1942.

creatropic" action on the islets of Langerhans. Lawrence and Young<sup>90</sup> failed to substantiate this claim in studies on diabetic persons and on dogs made permanently diabetic by injection of extracts of the anterior lobe. Marks and Young<sup>91</sup> did not find Collip's extract "significantly pancreatropic when administered to rats either by subcutaneous injection or by mouth." Although these same investigators found various crude pituitary extracts capable of increasing the insulin content of the rat pancreas, they stated that the pancreatropic factor was "probably not a hormone" and not identical with the lactogenic, the gonadotropic, the thyrotropic or the glycotropic substance.

Houssay and his co-workers<sup>86</sup> reported that the pancreas of hypophysectomized dogs was capable of normal secretion of insulin. Griffiths<sup>92</sup> claimed that in hypophysectomized rats, both the decrease in pancreatic content of insulin postoperatively and the increase in this content after the administration of extracts of the anterior lobe of the pituitary were proportional, respectively, to the loss of body weight, on the one hand, and to the gain in body weight, on the other. He discounted the presence of a specific insulin-increasing hormone in the anterior lobe of the pituitary gland.

*Metabolism of Proteins and Fats*—Little of significance has been added to the literature concerning the influence of the anterior lobe of the pituitary on the metabolism of fats and proteins.

The more recent work on the relation of the anterior lobe to protein metabolism in connection with body growth has already been discussed.

The consensus seems to be that extracts of the anterior lobe are capable of inducing nitrogen retention in the body tissues of animals receiving injections of this material.<sup>93</sup>

Several investigators in the past have reported that certain extracts of anterior pituitary had marked effects on fat metabolism of experimental animals. Sykes, Meuleman and Huffman<sup>94</sup> recently reported that a preparation of anterior lobe possessing marked liver-fat activity affected fat production of the mammary glands of 3 dairy cows. Both the total fat produced and the percentage of fat of the milk were increased.

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90 Lawrence, R. D., and Young, F. G. Oral Anterior Pituitary Extract (Collip) in Diabetes, *Lancet* **2** 709-710 (Dec 7) 1940.

91 Marks, H. P., and Young, F. G. Pancreatropic Factor of the Anterior Pituitary Lobe, *Lancet* **2** 710-712 (Dec 7) 1940.

92 Griffiths, M. The Influence of Anterior Pituitary Extract on the Insulin Content of the Pancreas of the Hypophysectomized Rat, *J. Physiol.* **100** 104-111 (Aug 11) 1941.

93 Cuthbertson, D. P., Webster, T. A., and Young, F. G. Anterior Pituitary Gland and Protein Metabolism. I. Nitrogen-Retaining Action of Anterior Lobe Extracts, *J. Endocrinol.* **2** 459-467 (Sept) 1941.

94 Sykes, J. F., Meuleman, W. L., and Huffman, C. F. Changes in the Fat Percentage and Fat Yield of Dairy Cows with Injections of an Anterior Pituitary Preparation, *Endocrinology* **30** 217-220 (Feb) 1942.

the pituitary to carbohydrate metabolism. They concluded that the rise in the level of the sugar in the blood which was observed to occur within the first few days after the administration of extracts of the anterior lobe to animals had been started was due to extrapancreatic activity. Along with this effect the pituitary extracts damaged the islet cells of the pancreas, of course, this damage would be aggravated by the initial hyperglycemia. Damage to the islet cells might become so severe that their ability to secrete insulin would remain diminished after cessation of the injections of pituitary extract. In these instances, persistent diabetes mellitus would result. Houssay found that in many instances the diabetes gradually disappeared, along with reversal of the histologic changes which had been produced in the islet cells. However, in some instances, a permanent diabetic state was established. In these animals extensive degenerative changes were encountered in the pancreatic islands particularly in the beta type of cell.

Lukens and Dohan<sup>87</sup> also have reviewed the subject of pituitary diabetes in the cat, they confirmed Houssay's observations as to the mode of action of the extracts of the anterior lobe of the pituitary gland. They reported that recovery in these animals took place under dietary and insulin therapy.

A so-called "contra-insular" hormone has been claimed to antagonize the action of insulin. Himsworth<sup>88</sup> suggested that a substance such as the diabetogenic or contra-insular factor might be responsible for the resistance to insulin sometimes encountered in cases of diabetes mellitus.

Recently some doubts have appeared concerning the existence of a "pancreatropic" factor secreted by the anterior lobe of the pituitary gland, which previously had been reported to increase secretion of insulin by the pancreas. Marks and Young<sup>89</sup> have reported that certain extracts of the anterior lobe would increase the insulin content of the rat pancreas to almost twice normal values. Collip<sup>90</sup> claimed that a primary alcoholic extract of the anterior lobe "has a profound effect upon carbohydrate metabolism" when administered orally to diabetic organisms. By this statement he meant that oral administration of this extract was capable of reducing the levels of blood sugar in a fasting organism and also the total daily requirement of insulin in some cases of diabetes mellitus, in fasting animals he produced a lowering of the level of sugar in specimens of blood taken after the oral administration of the extract. He suggested that this effect on carbohydrate metabolism was mediated by a "pan-

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87 Lukens, F. D. W., and Dohan, F. C. 'Pituitary Diabetes in the Cat Recovery Following Insulin or Dietary Treatment, *Endocrinology* **30** 175-202 (Feb.) 1942

88 Himsworth, H. P. The Mechanism of Diabetes Mellitus, *Lancet* **2** 65-68 (July 8) 1930

89 Collip, J. B. An Anti-Diabetogenic Effect of a Primary Alcoholic Extract of Pituitary Tissue Administered Orally. *Canad. M. A. J.* **42** 109-113 (Feb.) 1940

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92 Griffiths, M. The Influence of Anterior Pituitary Extract on the Insulin Content of the Pancreas of the Hypophysectomized Rat, *J. Physiol.* **100** 104-111 (Aug. 11) 1941.

93 Cuthbertson, D. P., Webster, T. A., and Young, F. G. Anterior Pituitary Gland and Protein Metabolism. I. Nitrogen-Retaining Action of Anterior Lobe Extracts, *J. Endocrinol.* **2** 459-467 (Sept.) 1941.

94 Sykes, J. F., Meuleman, W. L., and Huffman, C. F. Changes in the Fat Percentage and Fat Yield of Dairy Cows with Injections of an Anterior Pituitary Preparation, *Endocrinology* **30** 217-220 (Feb.) 1942.

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87 Lukens, F. D. W., and Dohan, F. C. Pituitary Diabetes in the Cat Recovery Following Insulin or Dietary Treatment, *Endocrinology* **30** 175-202 (Feb.) 1942

88 Himsworth, H. P. The Mechanism of Diabetes Mellitus, *Lancet* **2** 65-68 (July 8) 1930

89 Collip, J. B. An Anti-Diabetogenic Effect of a Primary Alcoholic Extract of Pituitary Tissue Administered Orally, *Canad. M. A. J.* **42** 109-113 (Feb.) 1940

urine from normal pregnant women did not have such effect unless the patient was deprived of water, then she would excrete antidiuretic substance. Ham<sup>100</sup> likewise has found an antidiuretic substance in the urine of women in eclampsia. Mukherjee<sup>101</sup> studied the effect of the blood ultrafiltrates obtained in 50 unselected cases of toxemia during pregnancy on the melanophoric antidiuretic and vasopressor responses in animals. The blood filtrates from normal women failed to result in the "triple response" to any significant degree. The blood filtrates from patients with toxemia had the capacity to produce all three reactions. Mukherjee concluded that the concentration of posterior pituitary hormone in the circulation of patients who had toxemia was increased and also possibly these patients were hypersensitive to this hormone.

In favor of this suggestion that a hyperfunctioning posterior lobe of the pituitary gland might be a potent factor in the production of eclampsia too are these facts: 1. Hypertension is characteristic of eclampsia, and extracts of the posterior lobe are known to have vasopressor effects. 2. The blood volume in eclampsia has been shown to be low<sup>102</sup> and this effect has been reproduced in animals by the injection of pitressin in pressor dosage<sup>103</sup>. The blood volume in normal pregnant women is high<sup>103</sup>.

On the other hand in women dying of eclampsia the renal findings are striking and the pituitary changes difficult to evaluate<sup>104</sup>. Selye and Bassett<sup>105</sup> have pointed out that even though urine and blood of pregnant women contain an antidiuretic substance, this substance is not necessarily derived from the posterior lobe of the pituitary, estrogens, androgens and progesterone may produce antidiuresis. Ham<sup>100</sup> found this antidiuretic substance in normal pregnant women, as well as in eclamptic women, as have other investigators<sup>103</sup>.

Finally, the recent work of Smith and Smith,<sup>106</sup> who found increased gonadotropic substances from the anterior lobe of the pituitary in the

100 Ham, G. C., cited by Griffith, Kimbrough, Corbit and Roberts<sup>104</sup>

101 Mukherjee, C. Posterior Pituitary Factor in the Toxemias of Pregnancy, *J. Obst. & Gynaec. Brit. Emp.* **48** 580-609 (Oct.) 1941

102 Dieckmann, W. J., and Kramer, S. Edema in Pre-Eclampsia and Eclampsia, *Am. J. Obst. & Gynec.* **41** 1-16 (Jan.) 1941

103 Griffith, J. Q., Jr., Corbit, H. O., Rutherford, R. B., and Lindauer, M. A. Studies of Criteria for Classification of Arterial Hypertension. V. Types of Hypertension Associated with the Presence of Posterior Pituitary Substance, *Am. Heart J.* **21** 77-89 (Jan.) 1941

104 Griffith, J. Q., Jr., Kimbrough, R. A., Jr., Corbit, H. O., and Roberts, E. A Study of the Antidiuretic Factor Occurring in Normal Pregnancy, and the Experimental Production of an Apparently Similar Factor in Nonpregnant Animals, *Endocrinology* **30** 542-550 (April) 1942

105 Selye, H., and Bassett, L. Effect of Desoxycorticosterone and Testosterone on Water and Chloride Metabolism, *Proc. Soc. Exper. Biol. & Med.* **45** 272-277 (Oct.) 1940

106 Smith, G. V. S., and Smith, O. W. The Anterior Pituitary-Like Hormone in Late Pregnancy Toxemia, *Am. J. Obst. & Gynec.* **38** 618-624 (Oct.) 1939



## THE POSTERIOR LOBE OF THE PITUITARY

The neurohypophysis consists of three poorly defined regions (1) the neural lobe, (2) the infundibular stem, and (3) the median eminence. Weaver and Bucy<sup>95</sup> have discussed the anatomic relations of the posterior lobe in detail.

The so-called "posterior lobe hormones" include the pressor, anti-diuretic, oxytocic and melanophore-depressing principles. The pressor, antidiuretic and oxytocic hormones arise from the intrinsic elements of the neurohypophysis, the pituicytes.<sup>96</sup>

While the pituicytes are regarded as secretory elements, the function of the unmyelinated nerve fibers present is not clear. There is evidence that they may be concerned in a reflex connection between the vagus and the supraopticohypophyseal tract.<sup>97</sup>

Recent work has renewed interest in studies of the hormones of the posterior lobe in the body fluids. Gilman and Goodman<sup>98</sup> several years ago demonstrated that rats deprived of water would excrete the anti-diuretic principle of the posterior lobe. Recently considerable work has been done on the presence of the antidiuretic and the pressor principle in the body fluids, particularly in connection with their detection in eclampsia, hypertension and certain other diseases. Attempts have been made to associate these conditions with hypersecretion of the posterior lobe of the pituitary. For example, it has been shown that in eclamptic or preeclamptic patients therapeutic doses of preparations of the posterior lobe would produce an unusually marked rise in blood pressure and a concurrent decrease in the volume of urine. This observation has been interpreted to mean either that these patients already had an excessive amount of principles from the posterior lobe in circulation or that they were hypersensitive to them or possibly both.

Variability in the results obtained in assays of the blood and urine of these patients for factors of the posterior lobe has made the clinical applicability of these studies doubtful. Teel and Reid<sup>99</sup> reported that concentrates of urine from women with eclampsia or preeclampsia had marked antidiuretic effects when injected into rats. Concentrates of

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95 Weaver, T. A., Jr. and Bucy, P. C. The Anatomical Relationships of the Hypophysial Stem and Median Eminence, *Endocrinology* **27** 227-235 (Aug.) 1940

96 Geiling, E. M. K., and Oldham, F. K. The Neurohypophysis, *J. A. M. A.* **116** 302-312 (Jan. 25) 1941

97 Sattler, D. G. Vago-Neurohypophysial Pressor Reflex, *Proc. Soc. Exptl. Biol. & Med.* **44** 82-86 (May) 1940

98 Gilman, A., and Goodman, L. The Secretory Response of the Posterior Pituitary to the Need for Water Conservation, *J. Physiol.* **90** 113-124 (July 15) 1937

99 Teel, H. M., and Reid, D. E. Observations upon the Occurrence of an Antidiuretic Substance in the Urine of Patients with Pre-Eclampsia and Eclampsia, *Endocrinology* **24** 297-310 (March) 1939

posterior lobe<sup>109</sup> The anterior lobe likewise plays a role in water metabolism, possibly secreting a diuretic substance, even though a specific diuretic factor has not been isolated from the anterior lobe Complete hypophysectomy results only in transient diabetes insipidus, since the presence of a functioning anterior lobe, as well as inactivation of the posterior lobe, is essential for the maintenance of permanent maximal diabetes insipidus<sup>110</sup> Administration of extracts of anterior pituitary to hypophysectomized rats already recovered from the initial postoperative diabetes insipidus again resulted in diabetes insipidus

Although nasal insufflation of dry pituitary powder has been used successfully in the treatment of diabetes insipidus, attempts have been made to prolong the action of parenterally administered preparations by giving them in oil or with zinc sulfate<sup>111</sup> Thorn and Stein<sup>112</sup> reported that a single injection of pitressin tannate in oil was effective in controlling polydipsia and polyuria for twenty-four to forty-eight hours in 3 cases of diabetes insipidus They warned against overdosage because of the danger of water intoxication

Total thyroidectomy has relieved diabetes insipidus in experimental animals<sup>113</sup> and in human beings Blotner and Cutler<sup>114</sup> reported that thyroidectomy produced a marked and persistent (for five years at least) improvement in both the diabetes insipidus and the Parkinson's disease of 2 young men whose symptoms followed encephalitis However, in 1 case in which diabetes insipidus was considered idiopathic, thyroidectomy did not result in any benefit

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109 Baker, A B, and Craft, C B Bilateral Localized Lesions in the Hypothalamus with Complete Destruction of the Neurohypophysis in a Pituitary Dwarf with Severe Permanent Diabetes Insipidus, *Endocrinology* **26** 801-806 (May) 1940 Dandy, W E Section of the Human Hypophyseal Stalk Its Relation to Diabetes Insipidus and Hypophyseal Functions, *J A M A* **114** 312-316 (Jan 27) 1940

110 Schweizer, M, Gaunt, R, Zinken, N, and Nelson, W O The Role of the Adrenal Cortex and the Anterior Pituitary in Diabetes Insipidus, *Am J Physiol* **132** 141-149 (Feb) 1941

111 Greene, J A, and January, L E Diabetes Insipidus Treated by the Subcutaneous Administration of a Suspension of Pitressin Tannate in Oil, *J A M A* **115** 1183-1185 (Oct 5) 1940 Stephens, D J Zinc Salts and Oil in Prolongation of Therapeutic Effect of Pitressin in Experimental Diabetes Insipidus, *Proc Soc Exper Biol & Med* **44** 240-241 (May) 1940

112 Thorn, G W, and Stein, K E Pitressin Tannate Therapy in Diabetes Insipidus, *J Clin Endocrinol* **1** 680-687 (Aug) 1941

113 Mahoney, W, and Sheelan, D The Effect of Total Thyroidectomy upon Experimental Diabetes Insipidus in Dogs, *Am J Physiol* **112** 250-255 (June) 1935

114 Blotner, H, and Cutler, E C Total Thyroidectomy in the Treatment of Diabetes Insipidus, *J A M A* **116** 2739-2745 (June 21) 1941

blood and urine of eclamptic patients, directs attention away from the posterior lobe

Although several commercial preparations of the posterior lobe are available for clinical use, as yet none of the active principles has been isolated as chemically pure entities. Two fractions, pitressin and pitocin, have been separated in a highly purified state from pituitary extracts. Geiling and Oldham<sup>96</sup> have reviewed the present knowledge of the chemical properties of these substances in detail.

Some investigators have expressed the belief that the two factors exist as separate entities in the natural state. However, Rosenfeld<sup>107</sup> in recent studies of their sedimentation properties in the ultracentrifuge found evidence to indicate that the pressor and the oxytocic principle exist normally as relatively large molecules, which are broken down to smaller, physiologically active products by the ordinary methods of chemical extraction.

Briefly, pitressin elicits cardiovascular, respiratory, renal (diuretic-antidiuretic), intestinal and certain metabolic effects on oxygen consumption, pitocin elicits the oxytocic action. Both substances act as antagonists to insulin and produce hyperglycemia.

Clinically, the widest use of extracts of the posterior lobe is in connection with parturition and in the treatment of diabetes insipidus.

The response of the pregnant uterus to preparations of the posterior lobe depends largely on the nature of that ovarian, placental or anterior pituitary hormone the influence of which is predominant at the time of injection. During early pregnancy the human uterus does not respond to pitocin, presumably because of the inhibitory effect on luteal secretion. Later the reactivity of the uterine musculature to pitocin returns, probably because the estrogens render the uterus more responsive. During parturition the uterus is responsive, and it is at this time that posterior pituitary extracts have been used most extensively, principally for the control of postpartum bleeding in the third stage of labor. Its use during the first and the second stage of labor is not recommended, since rupture of the uterus, fetal asphyxia, fetal death, laceration of the cervix, secondary atony of the uterus and even maternal cardiac death from over-exertion have been reported.<sup>108</sup> Extracts of the posterior lobe are useful also in the prevention or control of hemorrhage during abortion.

Both clinical and experimental studies support the view that diabetes insipidus is due to loss or diminution in the antidiuretic factor of the

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107 Rosenfeld, M. The Native Hormones of the Posterior Pituitary Gland. The Pressor and Oxytocic Principles, *Bull. Johns Hopkins Hosp.* **66** 398-403 (June) 1940.

108 DeLee, J. B. The Use of Solution of Posterior Pituitary in Modern Obstetrics, *J. A. M. A.* **115** 1320-1324 (Oct. 19) 1940.

rate of recipient animals as well as prevent the usual rise in the basal metabolic rate following the administration of the thyrotropic principle. If the latter phenomenon were due to specific antithyrotropic immune bodies the antiserum should not be capable of reducing basal metabolic rates. Furthermore "antihormones" have been reported to be present in the serums of untreated animals and of normal human subjects. Thompson and his associates have raised the question as to whether the "antihormones" are true immune bodies or are normal constituents of the serum. Fellows Nutting,<sup>119</sup> however, has denied that human serum normally contains a substance which exerts an inhibitory effect on anterior pituitary extract of human beings when both are injected into experimental animals.

Rutherford and Griffith<sup>120</sup> reported a case in which a patient experienced recurrent episodes of polyuria and polydipsia without glycosuria after subtotal thyroidectomy. This patient was observed during one such episode, his serum when injected in animals rendered them refractory to the usual antidiuretic effect of extracts of posterior pituitary. During the period of spontaneous recovery from the attack the patient's serum contained an excessive quantity of an antidiuretic factor. The authors did not find any pitressin-inhibiting substance in the serums of 2 patients who had chronic diabetes insipidus.

### PITUITARY PREPARATIONS

Experimental preparations of the active principles of the anterior lobe have been developed in which those principles are present in relatively pure form. Among these substances which have been prepared in highly potent and only minimally contaminated form are the lactogenic, the growth-promoting, the thyrotropic and the adrenotropic factor. Although potent gonadotropic substances have been isolated, the Commission of Biological Standardization has not felt that complete separation into follicle-stimulating and luteinizing fractions was sufficiently assured to warrant establishing international standards for material from this source. None of the active substances of the anterior lobe has been prepared to similar degrees of purity.

A large number of preparations of the anterior lobe are on the market, but none of them has been accepted by the Council on Pharmacy and Chemistry of the American Medical Association because of the lack of suitable evidence that such preparations are of value in therapy. The

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119 Fellows Nutting, M D. The Antigonadotropic Hormones in Normal Human Blood Serum, *Endocrinology* **26** 369-376 (March) 1940.

120 Rutherford, R B, and Griffith, J Q, Jr. Pitressin-Inhibiting Substance in Serum of a Patient with Transient Diabetes Insipidus, *J Clin Endocrinol* **1** 916-917 (Nov) 1941.

## THE ANTIHORMONES

The so-called "antihormones," first described by Collip and Anderson<sup>115</sup> in 1934, deserve brief mention

Several investigators<sup>116</sup> have reported that in animals treated with thyrotropic substance first an increased basal metabolic rate and subsequently hypothyroidism occurred. At the latter stage the blood serum of the experimental animals was found to confer "immunity" to the effect of the thyrotropic principle when injected into other animals, that is, the animals were made refractory to the thyrotropic principle. After several months without injections of pituitary extracts the refractory animals again became susceptible to the thyrotropic principle. Such an antihormone effect also has been shown to develop toward the lactogenic,<sup>117</sup> the gonadotropic<sup>118</sup> and other pituitary factors. Because of the apparent transmissibility of immunity from a treated animal to an untreated one, given serum from the former, the refractoriness which develops in experimental animals receiving injections of pituitary extracts has been assumed to represent a true immune reaction due to the formation of antibodies. Thompson, Collip and Selye<sup>117</sup> have reported that the serum containing the "antihormone" (antithyrotropic factor) developing in treated animals was specific for the species of animal from which the pituitary extract was prepared, that is animals rendered refractory to material from the pituitary gland of sheep still would respond to material from the pituitary gland of pigs.

Clinical evidence does not lend support to the antihormone theory. In the first place, human subjects do not become refractory to long-continued therapy with any of several substances, including thyroid extract, insulin and adrenal cortical extract. In the second place, Thompson and his associates<sup>117</sup> have shown that the serum of animals which have become refractory to the thyrotropic principle will reduce the basal metabolic

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115 Collip, J. B., and Anderson, E. M. The Production of Serum Inhibitors to the Thyrotropic Hormone, *Lancet* **1** 76-78 (Jan 13) 1934

116 Werner, S. C. Antibody Nature of Refractoriness to Injections of Hypophyseal Extracts Containing Thyrotropic Hormone, *Proc Soc Exper Biol & Med* **34** 392-394 (April) 1936. Harington, C. R. and Rowlands, I. W. Fractionation of Antithyrotropic and Antigonadotropic Sera, *Biochem J* **31** 2049-2054 (Nov) 1937. Loeb, L., and Friedman, H. Long Continued Injections of Acid Extract of Anterior Pituitary on Thyroid Gland and Sex Organs, *Proc Soc Exper Biol & Med* **29** 172-174 (Nov) 1931. Cutting, W. C., Robson, G. B., and Emerson, K., Jr. Refractoriness from Pituitary Thyrotropic Extracts, *Endocrinology* **24** 739-740 (May) 1939.

117 Thompson, D. L., Collip, J. B., and Selye, H. The Anti-Hormones, *J. A. M. A.* **116** 132-136 (Jan 11) 1941.

118 Meyer, R. K., Kupperman, H. S., and Finerty, J. C. Increase in Gonadotropic Content of Pituitary Glands of Female Rats Treated with Antigonadotropic Serum, *Endocrinology* **30** 662-666 (May) 1942.

## Book Reviews

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**Ambassadors in White** By Charles Morrow Wilson Price, \$3 50 Pp 372,  
with illustrations New York Henry Holt & Co Inc 1942

The subtitle of this most interesting book is "The Story of American Tropical Medicine," belying somewhat the more catchy phrase "Ambassadors in White." The subtitle, in truth, tells the story more properly than does the main title. The ambassadors in white are Finlay of Cuba, Reed of Virginia, Gorgas of Alabama, Deeks of Canada and Noguchi of Japan, together with the people with whom they were connected and with whom they worked. About half of the book is devoted to short biographic sketches of these five men, the ambassadors in their tropical garb. The rest of the book has to do with life, sickness and disease in the tropics and in Central America. The book is prefaced by a historical review, in which, incidentally, the author brings out many interesting facts. Probably few physicians realize that the first hospital in the Western Hemisphere was opened eleven years after Columbus' epochal voyage. Hospitals were established in Puerto Rico, Cuba, Panama, Mexico, Chile, Colombia, Ecuador and Venezuela prior to the beginning of the seventeenth century, and twenty-seven years before John Harvard was born. The University of Mexico, Mexico City, had a chair of medicine. In 1538 the University of Santo Tomas, on the island of Santo Domingo, had started to teach medicine. A medical school was established in Lima, Peru, in 1621, antedating by many years the inauguration of formal medical teaching in the United States.

The biographies of the five heroes of the book are interesting and instructive. To most medical readers Gorgas is well known, as are his accomplishments and his life, the same may be said of Walter Reed and Noguchi, but Carlos Finlay, who for years prior to Reed's investigations advanced the theory of transmission of yellow fever by a vector, *Aedes aegypti*, is known only in a general way, while Deeks, of the United Fruit Company, is also known by name and reputation, but few persons know of his real accomplishments and his deeds. It is interesting to read about these two men who stand out as pillars in the story of medicine in the tropics. Deeks is responsible for the inauguration of sanitation and the fighting of disease on the United Fruit Company plantations. His accomplishments are altogether remarkable. To the United Fruit Company and to the Standard Oil Company Wilson pays tribute. These two great international business organizations in the tropics were motivated by an altruistic-economic desire to keep their employees well, they do and have done so. On the other hand, innumerable United States corporations in the past have gotten what they could get out of the Central American countries but have done nothing to advance the health of the natives and apparently have left behind them only ill feeling.

In the tropics of the Middle American countries the health conditions are distressing and deplorable, despite the fact that these countries per unit of population spend much more for public health than does the United States. The microscopic animal and vegetable life of the tropics grows freely and unrestrainedly, and as the vegetation is lush and rich, just so are the disease-carrying fungi and animal parasites unrestrained in their growth in an environment which gives them everything they need in the way of moisture, temperature and food. Then there are few physicians in these countries, and most of them have congregated in the larger cities, so the rural population does not have medical services except to a limited extent. The picture that Wilson paints is depressing, but education and enlightenment of the poor people are doing, and will do, much to combat the disease scourges which cause tropical inhabitants to die in early life or to become chronic invalids.

It might be said that the book is attractively written, reads easily and gives many data which are at the present time not only well worth while but of great

commercially available preparations are relatively crude in comparison with those developed experimentally. They usually contain significant amounts of several other factors besides the one for which they are intended to be used. Inert proteins usually are present also. Furthermore, it has been shown that the active substances of many of these preparations deteriorate on standing in solution. D'Amour,<sup>121</sup> with his co-workers, has demonstrated that preparations of the anterior lobe purchased in drug stores have little demonstrable activity.

Extracts of the posterior lobe of the pituitary gland containing the oxytocic and the pressor factor are well known to clinicians. Their uses have been outlined. A number of preparations containing both factors, as well as preparations containing each factor, have been accepted by the Council on Pharmacy and Chemistry.<sup>122</sup> Their source is the pituitary glands of slaughtered animals and they are assayed in terms of U. S. P. units. These are standardized to an international pituitary powder.

102 Second Avenue Southwest

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121 D'Amour, F. E. The Potency of Certain Commercial Hormone Preparations. Second Study, *Endocrinology* **26** 88-92 (Jan.) 1940.

122 Freed, S. C. Present Studies of Commercial Endocrine Preparations, *J. A. M. A.* **117** 1175-1182 (Oct. 4) 1941.

**Treatment in General Practice** By Harry Beckman M D Professor of Pharmacology Marquette University School of Medicine Fourth edition thoroughly revised Price \$10 cloth Pp 1015 Philadelphia W B Saunders Company, 1942

The fourth edition of this book contains much new material—so much indeed that it cannot be entirely listed by the reviewer. It should be enough to say that the work has been brought thoroughly up-to-date. When one finds mention of sulfamylguanidine and sulfacetamide one realizes the newness.

The book is divided into twenty-four general sections in which the treatment of various diseases is discussed. The author comments on the great wealth of contributions to the therapy of disease that have appeared in recent years and he speaks of the difficulty in selecting the worthwhile material but he has done an excellent job. He has shown his ability to retain the oldest forms of treatment when they are adequate as well as to evaluate properly the advantages (and disadvantages) of the sulfonamide compounds most recently introduced as therapeutic agents.

His good common sense and forthright criticism of unsound procedure are noticeable throughout the book. It must be difficult to inject a sense of humor into a solemn medical treatise but the author has done so and successfully too.

The book is well written and is easy and pleasant to read. Altogether the author has done remarkably well in putting a great deal of sound and worthwhile information into a relatively small space.

**Central Autonomic Regulations in Health and Disease** By Heymen R Miller M D with an introduction by John F Fulton M D Price \$5.50 Pp 440 Greene & Stratton Inc., New York 1942

This is a work for which many clinicians have been waiting. The author well qualified for the task presents the principal evidence bearing on the relation of hypertension disturbances of metabolism and other diseases to disturbances especially central disorders of the autonomic nervous system. All fields of medicine as the author writes especially those of internal medicine and neurology impinge on a common territory here—a common ground of central autonomic regulations.

After a brief introduction which relates to the general physiology of the autonomic nervous system the author considers in turn the part played by this system in maintaining the homeostasis of body temperature metabolism circulation respiration and other phases of human physiology and disease. The response of the autonomic nervous system to pharmacodynamic substances receives attention in later chapters and discussion of anatomic aspects at the end provides a satisfactory and interesting means for summarizing the material as a whole.

Complete documentation as well as impartial consideration of opposing interpretations adds greatly to the value of this work. The book can be highly recommended.

**The Surgery of Pancreatic Tumors** By Alexander Brunschwig Pp 397 123 illustrations and 1 color plate St. Louis C V Mosby Company 1942

Written with the view of dealing with relatively few facts in a newly developed field and thus serving to stimulate further work in this field this monograph represents the author's attempt to record the cumulative experiences in the surgery of all types of pancreatic tumors. The book is divided into twenty-seven chapters the first few of which are devoted to the historical development of the subject, the embryologic anatomic and physiologic aspects of the pancreas experimental studies diagnostic procedures and preoperative and postoperative care. Four chapters are concerned with benign and with malignant pancreatic cysts and four chapters with benign and with malignant tumors of the ampulla of Vater. The remaining chapters deal with solid tumors of the pancreas especially the malignant forms. An extensive bibliography arranged alphabetically



value to members of the medical profession and more particularly to the physicians who may have to serve in the armed forces of the United States in these tropical countries

**Advances in Internal Medicine** Edited by J. Murray Steele, Vol. 1 Price \$4.50 Pp. XI + 292, with 16 illustrations New York Interscience Publishers, Inc., 1942

Recently a tabulation was made of the age distribution of physicians in the United States. Nearly half of them, it appears, are less than 45 years old. Thus, if a mathematical formula can be applied to the writing of medical books, half of them should be compiled for the benefit of the younger men and insofar as possible by them.

Usually this is not the case. The modern multiauthored textbooks tend to be written by older men in what Sir Andrew Clark termed the "cakes-and-ale" stage of their careers. Perhaps this lends experience and dignity to the printed result, but at the same time the stimulating flavor of youth is lacking.

The first volume of "Advances in Internal Medicine" is particularly noteworthy because of its ten contributors the most venerable is 45 years old and several are still on the right side of 35. The purpose of the series is to supply from time to time an informal summary of progress in those fields of internal medicine in which progress has recently occurred. The topics in volume 1 are well chosen to carry forward this idea. They include the use of the Miller-Abbott tube, of insulin and protamine insulin and of sulfonamide compounds in the treatment of infection, to be up to date and sailing with the prevailing medical wind, the volume includes discussions of current ideas on hypertension, riboflavin deficiency and nephrosis.

The result is a satisfactory book, readable, authoritative and, above all, youthfully vigorous. If the editor continues to collect for the ensuing volumes of the series an equally alert and capable group of young writers, his venture will be successful. Physicians in practice will like it. But more particularly the eighty-odd thousand medical students and young practitioners for whom the series is really designed will feel that they are being spoken to by their favorite and most stimulating instructors in just the manner they most enjoy.

**The Electrocardiogram and the X-Ray Configuration of the Heart** By Arthur A. Master, M.D., Cardiologist to the Mount Sinai Hospital, Assistant Professor of Clinical Medicine, Columbia University. Second edition enlarged and revised. Price, \$7.50 Pp. 404, with 163 illustrations Philadelphia Lea & Febiger, 1942

The same painstaking effort that went into the first edition of this book may be found in the revised and enlarged second edition. New material has been added. New sections deal with visualization of the chambers of the heart, disease of the tricuspid valve, myxedema and the "giant left auricle." The book covers rather thoroughly the effect of various types of cardiovascular disease and disorders on the cardiac silhouette. Each type of disease or disorder is illustrated by a roentgenogram of the heart. Beside each roentgenogram is placed an electrocardiogram. Each electrocardiogram is interpreted in the light of knowledge gained by the roentgen study plus a clinical study of the patient. The photographs and illustrations, which make up virtually the entire book, are excellent.

The main criticism of the book centers around the author's overenthusiastic interpretation of the electrocardiograms. The reader is left with the impression that in a given case one might learn the whole story by a careful study of the tracing alone. Numerous instances of this broad interpretation occur throughout the book. For example, the electrocardiograms in figures 49A and 82A are similar, indeed. Yet one is shown as the curve characteristic of rheumatic heart disease with mitral stenosis and insufficiency, while the other represents the curve characteristic of exophthalmic goiter.

With the exception of the excess of enthusiasm in the interpretation of tracings, the book is excellent.

## ANGINA PECTORIS AND THE SYNDROME OF PEPTIC ULCER

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In previous communications<sup>1</sup> we described certain relations between the syndrome of angina pectoris and that of peptic ulcer and called attention to certain clinical patterns. 1 The symptoms of peptic ulcer and anginal symptoms may occur suddenly and simultaneously, and occasionally acute peptic ulcer may be associated with coronary thrombosis. 2 Repeated attacks of angina pectoris at rest, finally eventuating in coronary thrombosis, may occur two to three hours after meals and during the night at the hours characteristic of pain from ulcer. 3 When symptoms of angina pectoris and peptic ulcer coexist, successful treatment for symptoms of ulcer may cause remission of the anginal syndrome. 4 Epigastric localization of anginal pain may be conditioned by a preexisting peptic ulcer.

In this paper we shall attempt an explanation of these phenomena and record additional illustrative cases. The common denominator that immediately suggests itself is a simultaneous disturbance in blood flow in the coronary and in the gastric and duodenal arteries. Evidence has been adduced that the arterial architecture of the stomach and duodenum plays a role in the localization of ulcers at the sites of election. Both Reeves<sup>2</sup> and Jatrou<sup>3</sup> showed that peptic ulcers occur by preference in areas where the arterial supply is poor and where anastomoses of the marginal arterial loops are few. The role of arteriosclerosis in the genesis of some peptic ulcers in older persons is generally accepted. It seems probable that the occasional simultaneous occurrence of coronary thrombosis and acute or penetrating peptic ulcers can be explained by simultaneous arterial occlusions in both territories induced by the same systemic causes. Or else shock resulting from closure of an artery in one area may induce secondary thrombosis in the other one. Cases 1 and 2 fall into this category. But this mechanism is rarely operative.

During the past twenty-five years the understanding of coronary arteriosclerosis and its role in the causation of the anginal syndrome and of myocardial necrosis has been greatly clarified. Investigators have learned that anginal pain is caused by myocardial anoxemia due to insufficient flow of blood through the coronary arteries. They have been so impressed by the pathologic changes in the

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1 Boas, E. P., and Levy, H. Angina Pectoris and the Peptic Ulcer Syndrome, *J. Mt. Sinai Hosp.* 8:422, 1942. Boas, E. P., in discussion on Walsh, B. J., Bland, E. F., Taquini, A. C., and White, P. D. The Association of Gall Bladder Disease and of Peptic Ulcer with Coronary Disease. A Post-Mortem Study, *Am. Heart J.* 21:697, 1941.

2 Reeves, T. B. A Study of the Arteries Supplying the Stomach and Duodenum and Their Relation to Ulcer, *Surg., Gynec. & Obst.* 30:374, 1920.

3 Jatrou, S. Ueber die arterielle Versorgung des Magens und ihre Beziehung zum Ulcus ventriculi, *Deutsche Ztschr. f. Chir.* 159:196, 1920.

is placed at the end of the book. The illustrations, consisting of photographs and line drawings, are profuse, well selected and instructive. In this monograph which is undoubtedly the most comprehensive consideration of the subject to date, the author fulfills his purpose thoroughly and successfully.

**Die Thrombocyten des menschlichen Blutes und ihre Beziehung zum Gerinnungs- und Thrombosevorgang** By A. Fomo and J. Schwendener. Pp. 130, with 112 illustrations. Berne: Hans Huber, 1942.

Professor Fomo, whose studies on blood platelets have been continuously appearing since 1911, has, with an associate, summarized in a small concise monograph his recent efforts to visualize the process of coagulation with an ultra-microscope under dark field illumination. There are truly remarkable photographs of the resting and the irritated thrombocyte, of the growth of pseudopodia, of the agglutination of platelets followed by the liberation of vesicles containing thrombokinasase and, finally, of the precipitation of needles of fibrin as the end point of thrombosis. This work is all the more remarkable as it provides a morphologic basis for physicochemical phenomena. It proves that purely morphologic investigations, undertaken with improved techniques, still play an important part in the furthering of knowledge. The senior author, who is professor of surgery at the University of Bern, does not draw any practical conclusions from his studies; he seemingly wished to emphasize the central role of the blood platelet in the process of thrombosis.

**Love Against Hate** By Karl Menninger, M.D. Price, \$3.50. Pp. 311. New York: Harcourt, Brace & Company, 1942.

Dr. Menninger's thesis, in brief, seems to be that the restrictions which have grown up under the customs and manners of "civilization" serve early to inculcate hate as a dominant trait of human character. The infant forced to nurse at regular hours and annoyed by attempts to train the excretory habits soon comes to hate his mother. Ingrained hates also develop in women, frustrated in all sorts of ways. The devotee of chess is really a father hater, he is pursuing a dominating male character, the king. This universal hate, if the reviewer understands the author correctly, has much to do with the disabilities of modern life, including the promotion of war. Love, fostered by work and by play, is set forth as an antidote. The reviewer does not follow Dr. Menninger in all the ramifications of his thesis, but he agrees that material and mechanical advances have not solved the problem either of human happiness or of behavior. Idealism, the mystical appreciation of intangible values, seems to be necessary, as is clearly realized by all great prophets to preserve man from being evolution's failure.

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## News and Comment

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**Hermann M. Biggs Memorial Lecture**—Lieut. Col. Paul F. Russell will deliver the Hermann M. Biggs Memorial Lecture on Thursday, April 1, 1943 at 8:30 p. m. in Hosack Hall, New York. The title of the lecture will be "Malaria and Its Influence on World Health." The lecture is to be given under the auspices of the Committee on Public Health Relations of the New York Academy of Medicine and will be open to the public.

thage in the stomach and duodenum, particularly in the region of the pylorus. When the vagal action was augmented by administration of physostigmine, all of the lesions were more marked, and actual ulcers were found in the pylorus. Hall, Ettinger and Banting<sup>13</sup> produced lesions of the myocardium and of the coronary arteries by long-continued daily administration of acetylcholine (activator of the vagus nerve) to dogs.

Several observers have reported that patients with disease of the coronary arteries exhibit cardiac slowing from pressure on the carotid sinus more frequently and to a greater degree than do normal persons.<sup>14</sup> This suggests increased sensitivity of the vagus nerve.

Hochrein and Schleicher<sup>15</sup> called attention to the association of peptic ulcer and angina pectoris and suggested that underlying many symptoms in both conditions, as well as their concurrence, is an altered tonus of the vegetative nervous system, particularly vagotonia.

Von Bergmann<sup>16</sup> and his school, and many others, have stressed the importance of disturbances of the vegetative nervous system in the etiology and the symptomatology of peptic ulcer and have pointed out that functional disturbances of the gastrointestinal tract may induce the same symptoms as do true ulcers. Indeed, they have expressed the belief that one cannot draw a sharp line of demarcation between the organic lesions and the functional disturbances. The syndrome of peptic ulcer is often encountered without roentgen evidence of gastrointestinal ulceration, and many patients with disease of the coronary arteries and with symptoms of peptic ulcer have no ulcer demonstrable on roentgen examination. Kaufmann<sup>17</sup> suggested that the periodicity of symptoms and clinical manifestations in patients with ulcer are due to periodic changes in activity of the vagus nerve.

The syndromes of peptic ulcer and angina pectoris have many similarities. Both conditions affect males predominantly, and both have a definite familial distribution. Angina pectoris, as well as peptic ulcer, is rarely encountered in Negroes.<sup>18</sup> More significant, probably, is the periodicity of symptoms in both conditions, the alternation of states of activity and remission. Periodicity of symptoms is well recognized in the syndrome of peptic ulcer and is indeed of great diagnostic value. It is not widely recognized that the anginal syndrome frequently exhibits similar alterations of activity and freedom from pain. Anginal symptoms may reappear suddenly after the patient has been without pain for months or years. Sometimes this is due to fresh arterial and myocardial lesions, at times anginal pain may recur on effort without evident development of fresh lesions and with no recognizable cause. In both disease states the symptoms tend to recur during periods of emotional stress.

Angina pectoris, like the pain from peptic ulcer, frequently awakens the patient from sleep during the night. During sleep there is increased activity of the vagus

13 Hall, G. E., Ettinger, G. H., and Banting, F. G. An Experimental Production of Coronary Thrombosis and Myocardial Failure, *Canad. M. A. J.* **34**: 9, 1936.

14 Braun, L., and Samet, B. Zur klinische Bedeutung des "Vagusdruckes," *Wien klin. Wchnschr.* **40**: 1383, 1927. Weiss, S., and Baker, J. P. The Carotid Sinus Reflex in Health and Disease, *Medicine* **12**: 297, 1933. Mandlestamm, M. E. Vegetative Cardiac Reflexes and Angina Pectoris, *Vruch gaz.* **35**: 741, 1931.

15 Hochrein, M., and Schleicher, I. *Ulcus pepticum und Angina pectoris*, *Munchen med. Wchnschr.* **88**: 328, 1941.

16 von Bergmann, G. *Ulcus Pepticum*, in von Bergmann, G., Staehelin, R., and Salle, V. *Handbuch der inneren Medizin*, ed. 3, Berlin, Julius Springer, vol. 3, pt. 1, p. 524.

17 Kaufmann, J. Bemerkungen über die pathologische Bedeutung der Funktionsstörungen des Magens, *Arch. f. Verdauungskr. (suppl.)* **19**: 85, 1913.

18 Boland, F. K. Peptic Ulcer and Diseases of Biliary Tract in Southern Negro Influence of Diet, *Ann. Surg.* **102**: 724, 1935.

coronary arteries that they have paid little attention to the functional changes in the coronary circulation that may also give rise to anoxemia of the heart muscle. In recent years it has been shown that myocardial infarction may result from transient coronary insufficiency in a patient with diseased coronary arteries. This insufficiency may be due to hemorrhage, shock or any physical strain that leads to an imbalance between the oxygen needs of the heart muscle and the capacity of the diseased coronary arterial bed to deliver to the heart muscle sufficient oxygen-carrying blood.

There is as yet little recognition of the role of reflex coronary vasoconstrictor factors in the genesis of the anginal syndrome and of myocardial infarction. Heberden,<sup>4</sup> in his original description of angina pectoris, called it a spasmodic complaint and pointed out that "its attacks are often after the first sleep, which is a circumstance common to many spasmodic disorders." Roberts<sup>5</sup> emphasized the importance of psychogenic and neurogenic factors in the production of the anginal syndrome. More recently one of us<sup>6</sup> called attention to reflex mechanisms in certain coronary syndromes.

The significance of vasomotor changes of the caliber of the coronary arteries in the clinical syndromes of coronary artery disease has been reviewed by Gilbert.<sup>7</sup> Vasoconstrictor impulses reach the coronary arteries through the vagus nerve. Dietrich and Schweigel<sup>8</sup> in von Bergmann's laboratory found that distention of the stomach with a rubber balloon caused a marked decrease in coronary flow. This effect was abolished by section of the vagus nerve or by administration of atropine. These experiments were confirmed by Gilbert, Fenn and LeRoy.<sup>9</sup> Distention of the dog's stomach at the esophageal orifice has the greatest effect in reducing coronary flow. This observation may throw some light on the common association between hiatal hernia and angina pectoris. Gilbert, in a roentgen study of 44 patients with angina pectoris, discovered hiatal hernia in 17 per cent. These experiments also offer an explanation for the occurrence of angina pectoris with diverticula of the lower part of the esophagus and for angina pectoris induced by swallowing.<sup>10</sup> Swalm and Morrison<sup>11</sup> recorded cases in which distention of the esophagus caused anginal pain and changes in the RT segment of the electrocardiogram as well as extrasystoles.

Manning, Hall and Banting<sup>12</sup> carried out prolonged electrical stimulation of the vagus nerve in dogs. At autopsy they repeatedly found capillary congestion and hemorrhage in the heart, some early hyaline degeneration in the cardiac muscle and infarcted areas in the anterior papillary muscle. Changes in the form of the T wave were constant. In addition, there was marked congestion with hemoi-

4 Heberden, W. Commentaries on the History and Cure of Diseases, Boston, Wells & Lilly, 1818, p. 296.

5 Roberts, S. R. Nervous and Mental Influences in Angina Pectoris, *Am Heart J* 7 21, 1931.

6 Boas, E. P. Some Immediate Causes of Cardiac Infarction, *Am Heart J* 23 1, 1942.

7 Gilbert, N. C. Influence of Extrinsic Factors on the Coronary Flow and Clinical Course of Heart Disease, *Bull New York Acad Med* 18 83, 1942.

8 von Bergmann, G. Das "epiphrenale Syndrom," seine Beziehung zur Angina pectoris und zum Kardiospasmus, *Deutsche med Wchnschr* 58 605, 1932.

9 Gilbert, N. C., Fenn, G. K., and Le Roy, G. V. The Effect of Distention of Abdominal Viscera on Coronary Blood Flow and Angina Pectoris, *J A M A* 115 1962 (Dec 7) 1940.

10 Edeiken, J. Angina Pectoris and Spasm of the Cardia with Pain of Anginal Distribution on Swallowing, *J A M A* 112 2273 (June 3) 1939.

11 Swalm, W. A., and Morrison, L. M. Relation of Gastro-Intestinal Disorders to Angina Pectoris and Other Acute Cardiac Conditions, *Rev Gastroenterol* 6 41, 1939.

12 Manning, F. W., Hall, G. E., and Banting, F. G. Vagus Stimulation and the Production of Myocardial Damage, *Canad M A J* 37 314, 1937.

The histories presented in this paper, interpreted in the light of the foregoing discussion, suggest that the common denominator of the syndromes of angina pectoris and peptic ulcer is heightened excitability of the vagus nerve. Symptoms of peptic ulcer may arise from vagal activity in the stomach, and symptoms of angina pectoris may result from vagal coronary vasoconstriction. A functional disturbance of one organ may reflexly, via the vagus nerve, induce a disorder in the other. This train of events is illustrated in case 3, in which angina pectoris appeared with recurrence of a gastric ulcer, and in cases 6 and 7 with "ulcer timing" of the anginal seizures. More often a constitutionally determined heightening of tone or excitability in the vagus nerve seems to be responsible for simultaneous dysfunction of both the stomach and the heart. Cases 1, 2 and 5 illustrate this condition. Some day investigation may disclose what role, if any, the acetylcholine mechanism plays in these states of heightened activity of the vagus nerve.

Patients with angina pectoris, as a rule, walk with greater difficulty after eating because anginal pain is more readily induced. It is caused by the increased work imposed on the heart by the digestive process as well as by the reflex coronary constriction resulting from gastric distention and contraction. Gilbert, Fenn and LeRoy<sup>9</sup> succeeded in abolishing or lessening this greater susceptibility to anginal pain after eating by giving atropine. Some patients with the combined syndromes of peptic ulcer and angina pectoris walk more freely and farther after a meal (case 4). In these patients anginal pain developing on effort is a product of the various forces operative at the moment. Whether the patient can walk more freely when the stomach is full or when it is empty will depend on which influence is the stronger, the vasoconstrictor effect on the coronary arteries, conditioned reflexly by the gastric distention induced by the meal, or the inhibition of the hunger contractions by the introduction of food into the stomach and the consequent reduction of afferent impulses or of vagal tone.

Patients with the combined syndromes of peptic ulcer and angina pectoris when treated for the symptoms of peptic ulcer often report relief from the anginal seizures. Such patients should receive a modified Sippy diet or some other suitable diet, with frequent feedings. In addition they should receive full doses of atropine, enough to induce dryness of the mouth, this necessitates giving from  $\frac{1}{150}$  to  $\frac{1}{75}$  grain (0.43 to 0.86 mg.) three or four times a day. One-third to  $\frac{1}{2}$  grain (0.022 to 0.032 Gm.) of phenobarbital given three times a day lessens reflex excitability. In some cases alkalis or colloidal aluminum hydroxide may be useful, in others these drugs seem to be of less value.

Glyceryl trinitrate should be used freely for postprandial pain, no matter where the pain is located. At times erythrol tetranitrate,  $\frac{1}{2}$  to 1 grain (0.032 to 0.06 Gm.) given four times a day, is helpful. Theophylline with ethylene diamine in our experience gives no relief and may aggravate symptoms by irritating the stomach.

The rigidity with which this regimen should be carried out and the duration of treatment vary from case to case. In the presence of a peptic ulcer or of symptoms suggesting advanced coronary narrowing and imminent coronary occlusion treatment must be prolonged. If it is suspected that coronary closure is occurring—and this can be judged only by the frequency of the pain and the readiness with which it comes on—the patient should be put to bed and treated as though he had coronary thrombosis. Sudden change in the provoking causes of anginal pain, with change from angina pectoris after effort to anginal attacks at rest, indicates a progressive lesion in the coronary arteries and heralds the development of cardiac infarction. Rest, the use of vasodilators and an ulcer regimen may relieve the coronary insufficiency in these cases and allow the establishment of sufficient collateral circulation to enable the patient to survive the closure of the

nerve Carlson<sup>19</sup> noted that hunger contractions of the stomach are often more vigorous during sleep, presumably because of relative overactivity of the vagus nerve in consequence of the elimination of all inhibitory influences that pass over the splanchnic nerves, Schmidt<sup>20</sup> attributed the frequent occurrence of visceral colic during sleep to overactivity of the vagus nerve Klewitz<sup>21</sup> and Messerle<sup>22</sup> observed prolongation of the PR interval during sleep Boas and Goldschmidt<sup>23</sup> described marked reduction of heart rate together with development of pronounced sinus arrhythmia during sleep All these are evidences of increased vagal activity

In 1939 Weinstein and Mattikow<sup>24</sup> reported 2 cases in which anginal attacks developed before meals and in which the appearance of angina was associated with hypoglycemia Administration of dextrose promptly relieved the anginal seizures One of the patients had severe angina on walking before meals and could exert himself more readily after having eaten Both patients were treated with low carbohydrate, high protein diets and were relieved of their anginal pain Sandler<sup>25</sup> presented evidence to show that sudden spontaneous lowering of blood sugar may induce anginal attacks and that patients may be relieved of their spontaneous anginal attacks by diets that combat great fluctuation of blood sugar levels It is known that overdosage with insulin may induce anginal pain and electrocardiographic changes Peskin<sup>26</sup> reported the cases of patients with recurrent abdominal pain simulating peptic ulcer and associated with relative hypoglycemia, whose pains were relieved by diets low in carbohydrate

Himwich and his associates<sup>27</sup> showed that acute hypoglycemia in dogs gives rise to a picture of widespread autonomic stimulation with initial preponderance of sympathetic activity and subsequent evidence of parasympathetic activity Vagal effects noted were progressive slowing of the heart and prolongation of the PR interval After section of the vagus nerve, these phenomena did not appear Other authors<sup>28</sup> have described an increase of gastric motility and of secretion resulting from hypoglycemia induced by large doses of insulin

Bender and Siegal<sup>29</sup> showed that acetylcholine or some similar agent is released in the body in response to hypoglycemia induced with insulin We have examined the blood sugar levels in a number of patients with the combined syndromes of ulcer and anginal pain but have discovered no hypoglycemia However it seems probable that this mechanism may be active in some of the cases

19 Carlson, A. J. *The Control of Hunger in Health and Disease*, Chicago, University of Chicago Press, 1916, vol. 7, p. 150

20 Schmidt, R. *Die Schmerzphänomene bei inneren Krankheiten, ihre Pathogenese und Differential Diagnose*, ed. 2, Leipzig, W. Grau-Müller, 1910, p. 62

21 Klewitz, F. *Der Mechanismus der Herzreaktion im Schlaf*, *Deutsches Arch. f. klin. Med.* **101** 267, 1919

22 Messerle, N. *Ueber den Einfluss des extrakardialen vegetativen Nervensystems auf das Elektrokardiogramm*, *Ztschr. f. d. ges. Neurol. u. Psychiat.* **117** 499, 1928

23 Boas, E. P., and Goldschmidt, E. F. *The Heart Rate*, Springfield, Ill., Charles C. Thomas, Publisher, 1932, p. 81

24 Weinstein, J., and Mattikow, B. *Angina Pectoris as a Predominating Symptom in Spontaneous Hypoglycemia*, *Ann. Int. Med.* **12** 1886, 1939

25 Sandler, B. P. *The Control of the Anginal Syndrome with a Low Carbohydrate Diet*, *M. Ann. District of Columbia* **10** 371, 1941

26 Peskin, A. R. *Hypoglycemia with Paradoxical Sugar Tolerance Curve Simulating Peptic Ulcer*, *J. A. M. A.* **108** 1601 (May 8) 1937

27 Himwich, H. E., Martin, S. J., Alexander, G. A. D., and Fazekas, J. F. *Electrocardiographic Changes During Hypoglycemia and Anoxemia*, *Endocrinology* **24** 536, 1939

28 Fortuyn, J. D. *Hypoglycemia and the Autonomic Nervous System*, *J. Nerv. & Ment. Dis.* **93** 1, 1940

29 Bender, M. P., and Siegal, S. *Release of Autonomic Humoral Substances in Hypoglycemic Cats and Monkeys*, *Am. J. Physiol.* **128** 324, 1940

CASE 2—This instance was reported in detail elsewhere<sup>30</sup> as the case of a man who at the age of 49 had a sudden onset of pain suggesting ulcer, as well as of anginal pain, in whom electrocardiography revealed an infarct of the anterior aspect of the left ventricle and roentgen examination disclosed a penetrating gastric ulcer of the reentrant angle

In both cases 1 and 2 organic lesions of the heart and the stomach developed simultaneously. Brooks<sup>31</sup> described a case in which the diagnosis of coronary thrombosis was made and in which a perforated peptic ulcer was suspected. At autopsy both acute coronary thrombosis and a perforated duodenal ulcer were found

#### *Angina Pectoris with Recurrence of Gastric Ulcer*

CASE 3—A man, B L., at the age of 38 complained for several months of epigastric pain radiating through to the back, occurring one hour after meals. Roentgen study disclosed a gastric ulcer. The symptoms remitted for over eight years but recurred when the patient was 46 years old. The pain was similar, occurring in the epigastrium about one hour after meals. He then, for the first time, noted a squeezing pain in the anterior part of the chest, which radiated to the epigastrium, occurring one hour after meals and lasting about one to two hours at a time. He walked less readily than previously. After 3 blocks he would become fatigued and would then experience midchest pain radiating straight through to the back, compelling him to rest, which led to relief.

Physical examination at this time disclosed a well built man. The lungs were clear, some epigastric tenderness was present. Fluoroscopic study revealed a heart of normal size and configuration, the heart sounds were of good quality. The blood pressure was 190 systolic and 110 diastolic. The electrocardiogram showed no significant abnormalities.

The next year, at the age of 47, he had a recurrence of his symptoms of ulcer, and roentgen examination again showed a gastric ulcer. He was given an appropriate diet and remained well until the next year, when he complained of pain in the right lower region of the chest, occurring at irregular intervals. This pain was unrelated to meals or effort, but after walking quickly on an upgrade he would become fatigued and would be compelled to rest for several minutes. There was no recurrence of the epigastric midchest pain on walking.

Physical examination including electrocardiographic study showed little change. The blood pressure was somewhat lower, 150 systolic and 90 diastolic.

#### *Increased Capacity for Walking After Meals*

CASE 4—A man aged 54 had suffered for over twenty years from heartburn in the lower substernal area, occurring one to two hours after meals and relieved by alkali. The pain would remit for several years at a time. No gastrointestinal roentgenograms were taken.

At the age of 50 he experienced a sudden attack of palpitation associated with very slight midsternal pain several hours after breakfast, while being shaved. There was no breathlessness. One hour later the sinus rhythm was regular, the heart rate was 80 beats per minute, the blood pressure was 138 systolic and 90 diastolic, the heart sounds were dull and there were no murmurs. An electrocardiogram taken on the following day showed a PR interval measuring 0.22 second and moderate lowering of the T waves in all leads.

During the next four years he continued at his work and felt quite well, he was able to walk freely at all times. At the age of 54 he began to experience pain in the left lower region of the chest and in the lower substernal area, occurring intermittently, chiefly three to four hours after meals, and relieved by food. One week after the onset of these symptoms, while walking he experienced epigastric pain radiating to the lower part of the chest and compelling him to rest. He was then given a Sippy diet with a powder. Epigastric pain on walking continued for three weeks, when weakness and very slight pain in the lower midchest region replaced the epigastric pain on walking. The pain in the chest was relieved by a short rest. During this time, embracing both phases of epigastric and thoracic pain on walking, he noted that he could walk more freely and greater distances on a full stomach. After he had been on the diet for five weeks, all his symptoms remitted, and he was examined two weeks later. The findings on general physical examination were unchanged, but an electrocardiogram taken at this time exhibited normal voltage of the T wave in leads I and II.

The foregoing history, in addition to pointing out the increased capacity for walking after meals, also illustrates the clinical appearance of previously silent

31 Brooks, H. Abdominal Signs and Symptoms of Thoracic Disease, *Rev Gastroenterol* 3 143, 1936



particular coronary artery whose progressive closure is at the root of the exacerbation of symptoms

Patients who have had peptic ulcer and who subsequently have disease of the coronary arteries may experience anginal pain on effort or the pain of coronary thrombosis only in the abdomen (patients in cases 9 to 13). In some cases the pain may start in the abdomen and radiate to the chest or the arms, in others it may commence in the chest and radiate to the abdomen. This distribution of pain may be due to reflexes initiated by the disturbance in the heart or, as we suggested in a previous paper,<sup>30</sup> the pain may simply travel along nerve pathways previously sensitized by the ulcer.

#### SUMMARY

Certain relations between the syndromes of angina pectoris and peptic ulcer are described. It is suggested that neurogenic mechanisms mediated by the vagus nerve are concerned in this association.

#### REPORT OF CASES

##### *Sudden Occurrence or Recurrence of Peptic Ulcer with Symptoms, Simultaneous Onset of Angina Pectoris with Electrocardiographic Evidence of Myocardial Damage*

CASE 1—A man, F. G., had meningitis at the age of 32. At the age of 47 a roentgenogram showed a penetrating peptic ulcer. The symptoms of ulcer persisted for some three years and then abated. At the age of 51, for a period of two months he was awakened regularly at 2 a. m. by a burning pain in the right lower region of the chest, radiating to the midthoracic part of the spinal column, which was relieved by taking alkaline powders. During this same period he experienced similar pain when walking in the cold.

The following year, at the age of 52, he had a recurrence for two months of similar nocturnal pain which lasted two or more hours at a time. These attacks were not relieved by the powders. During this time he was unable to walk more than three blocks because, regardless of the weather, he would experience pain in the lower substernal area and in the right lower region of the chest, compelling him to stop.

He was a thin man. There was no tenderness in the epigastrium. Fluoroscopic study revealed a heart normal in size and configuration. There was a systolic murmur at the apex. The blood pressure was 170 systolic and 100 diastolic. The electrocardiogram was normal.

He was referred to the Mount Sinai Hospital. There the hemoglobin content was found to be 95 per cent and the white blood cell count 9,300. The stool was negative to the guaiac test. A roentgen film showed a shallow pocket in the posterior wall of the stomach, high up on the lesser curvature. There was an incisura at the antrum. Gastroscopic inspection showed a small cleancut shallow ulcer about midway up on the lesser curvature. Subsequent roentgen examination revealed diminution in the size of the ulcer pocket. An electrocardiogram taken two weeks after the normal record obtained in the office showed partial inversion of the T wave in lead IV.

An ulcer diet and alkalis induced complete subsidence of his symptoms.

The following year, at the age of 53, he was readmitted to the hospital, complaining of intermittent claudication in both legs. At this time he mentioned no symptoms of ulcer or anginal symptoms but said that he had recently had pain in the right lower quadrant of the abdomen and diarrhea. A gastrointestinal roentgenogram taken at this time showed no abnormality. The spleen was felt 2 fingerbreadths below the costal margin. An electrocardiogram showed a diphasic, partially inverted T wave in lead IV.

The striking point in case 1 is the electrocardiographic change developing during a period of recurrence of the symptoms of ulcer and of coronary disease. The symptoms of peptic ulcer were the most striking, and differed from the symptoms of ulcer which the patient had described in previous years. First, the attacks in general were of longer duration—in fact, one attack lasted as long as five hours, second, for the first time the pains were not relieved by alkali, and, third, these symptoms of ulcer were associated with symptoms of angina on effort.

30 Boas, E. P., and Levy, H. Extracardiac Determinants of the Site and Radiation of Pain in Angina Pectoris with Special Reference to Shoulder Pain, *Am Heart J* 14:541, 1937.

*Repeated Anginal Attacks Occurring at Rest and Giving Warning of Impending Coronary Closure, Commonly Occurring One or Two Hours After Meals or at Night and Stimulating Peptic Ulcer in Their Timing and in the Location and Character of the Pain*

CASE 6—I S, a printer aged 43, was ill for ten weeks with fever and pain and swellings of joints. He had never experienced symptoms suggesting peptic ulcer. At the age of 50 he first noted heart burn, situated high in the epigastrium and radiating to the throat, occurring one to two hours after meals and lasting a few minutes. For six weeks these symptoms persisted, with remissions of a few days at a time. Then, one morning, heart burn again was felt at exactly the same hour. This time, however, it radiated to both shoulders and to the head and the neck, and lasted throughout the day, relieved but slightly by food. Following this prolonged attack, heart burn was regularly provoked by walking 5 or 6 blocks but did not compel him to rest. He continued at his work and was examined two weeks after the prolonged attack of heart burn.

He was a well built man of sallow complexion. The lungs were clear. There was no abdominal tenderness. Fluoroscopic study revealed a heart of normal size and configuration. The first heart sound was somewhat dull, a systolic murmur was audible at the apex. The blood pressure was 120 systolic and 75 diastolic. The electrocardiogram revealed Q waves and negative T waves in leads II and III. There was slight elevation of the RT segment in both these leads, indicating that the lesion was a recent one.

It is clear that this patient suffered coronary thrombosis two weeks previously and that the ulcer-like symptoms beginning six weeks before that were in the nature of premonitory symptoms. Do these represent repeated spasms of the coronary arteries leading finally to thrombosis? There is no evidence of an acute peptic ulcer or even of an ancient ulcer.

CASE 7—M S, a man aged 56, had had hay fever for several years. The symptoms of hay fever set in on Aug. 16, 1940. Three days later he was drenched in a rainstorm. The next morning he was loath to leave his bed and noted midsternal pain. During this day he suffered four or five attacks of pain in the middle of the substernal area, radiating to the left upper extremity, each attack lasting approximately ten minutes. He took to bed and for the next week experienced repeated attacks, the last one, two days before examination, was the most intense and lasted fifteen minutes. He had never experienced pain in the chest on walking.

Examination on August 29 revealed a well built man. The pupils reacted normally to light. The lungs were clear. Fluoroscopic study revealed a heart of normal size and configuration. The heart sounds were of good quality, there were no murmurs. The blood pressure was 160 systolic and 80 diastolic. The electrocardiogram showed a shallow diphasic T wave in lead I and a sharply inverted T wave in lead IV, evidences of a recent infarction of the anterior aspect of the left ventricle.

He remained in bed for two months, experiencing recurrent attacks, some severe enough to require morphine by hypodermic injection. Subsequently he noted that moderate effort, such as walking 3 blocks slowly, would provoke breathlessness and pain in the lower mid-thoracic region, compelling him to rest. When next seen, in June 1941, he stated that for the preceding four weeks he had suffered epigastric pain two hours after meals and that at 3 a. m. on the day of his visit he had been awakened by the same epigastric pain. He stated that he had never experienced such postprandial epigastric symptoms in the past. In view of the postprandial timing of the recent symptoms, the initial history was reviewed. When asked to enlarge on his original statement of "four or five attacks" of midsubsternal pain on the first day symptoms occurred, he remarked that attacks occurred at 4 a. m., 10 a. m., 3 p. m. and again at 3 a. m. (He had his breakfast at 8 a. m., lunch at noon, dinner at 6 p. m. and took no late supper.) During the following week the attacks referred to occurred at 3 a. m., awakening him from sleep.

Physical examination in June 1941 disclosed good heart sounds. The blood pressure was 161 systolic and 90 diastolic. The electrocardiogram showed a normal upright T wave in lead I and a diphasic T wave in lead IV.

In case 7 the periodicity of the initial symptoms, occurring during the phase of gradual coronary closure, was not recognized until the characteristic periodicity of symptoms occurring nine months later led to a review of the original symptomatology.

coronary disease, brought to light by recurrent symptoms of peptic ulcer. It shows too the remission of the anginal syndrome as the pain of peptic ulcer was relieved by medication and diet.

*Recurrence of Angina Pectoris with Onset of Symptoms of Peptic Ulcer, Delayed Development of Duodenal Ulcer*

CASE 5—A man, A. B., gave no history of previous abdominal symptoms. Nine months before he came for examination, at the age of 45, as he left his home one morning and started walking, he was seized by pressure in the lower part of the chest, reflected into both upper extremities, compelling him to halt. This anginal pain occurring only during the morning walk continued for four weeks. The pain then remitted completely for eight months, and during this time he felt entirely well. Then, two weeks before he came for examination, immediately after his usual noonday meal, he became dizzy and pale, and vomited. That evening epigastric pain without radiation was experienced. It lasted for some two hours and finally was relieved by magnesium hydroxide. Following this episode the epigastric pain recurred mornings at 11:30, it would then be relieved by taking lunch and would recur at 3:30 in the afternoon, beginning in the epigastrium, radiating to the lower part of the chest and lasting fifteen minutes. He would desist from his work for a few minutes and find relief. Three days before he was examined, at 9 a. m., one hour after breakfast, he experienced midabdominal pain, reflected to the lower part of the chest and lasting two hours. That night just before retiring, at midnight, he had severe midabdominal pain radiating to the lower part of the chest, where it was more intense, for a half hour. The following day three attacks were experienced, at 12 noon, at 4 p. m. and at midnight, each one lasting about twenty minutes. He complained of no pain in the chest on walking at this time.

He was a well built man of good color, the lungs were clear, there were no abdominal findings. Fluoroscopic inspection revealed a heart normal in size and configuration. The heart sounds were of good quality, there were no murmurs. The blood pressure was 130 systolic and 80 diastolic. The electrocardiogram was normal. It appeared clinically that the patient was suffering from angina pectoris and possibly peptic ulcer. He was given a modified Sippy diet and an alkali to take between meals. A gastrointestinal roentgenogram taken immediately after the examination showed no peptic ulcer. Thereafter he continued to experience diffuse pain in the upper abdominal region on the right and left sides, reflected to the upper dorsal region of the spinal column, chiefly at 9 p. m., three hours after dinner. Glyceryl trinitrate, while not immediately effective, reduced the duration of this pain from the usual thirty minutes to five minutes. At one time he had similar pain at 4 p. m., quickly relieved by this drug. The electrocardiogram taken six weeks after the first one showed no change.

Seven months later he had recurrent pain in the left hypochondrium, radiating to the lower part of the epigastrium, always at 10 a. m., two hours after breakfast, and at 4 p. m., four hours after lunch. At this time, walking 5 blocks would provoke pain in the left forearm with slight heaviness in the lower midthoracic region. Examination again showed no change in the electrocardiographic tracing. At Mount Sinai Hospital a barium sulfate meal showed a persistent deformity involving the distal third of the duodenal bulb. This was interpreted as the result of ulceration. There was also evidence of an irregular shadow encroaching on the magenblase in the region of the greater curvature. There was a 30 per cent residue in the stomach after six hours. Gastroscopic inspection failed to visualize any lesion in the esophagus or in the stomach. The Rehfuess test meal showed, during fasting, free acidity of 64, with total acidity of 75. With a soft diet, milk and cream, and medication with aluminum hydroxide, the symptoms gradually disappeared.

In case 5 the symptoms of peptic ulcer came on suddenly, with great severity, and were accompanied by symptoms of angina pectoris. Roentgen study, however, revealed no ulcer at the onset. We do not know how long it took for the ulcer to develop, but it was certainly a matter of weeks. The lesion was discovered at the first roentgen examination seven months later. The course of events here is analogous to that observed in patients with prodromal symptoms of coronary thrombosis, in whom anginal attacks may persist for weeks before there is objective evidence of coronary closure. Similarly, symptoms of peptic ulcer may come on suddenly with no roentgen evidence of ulceration. Only after a period of weeks may the ulcer be revealed by the roentgen rays.

heart burn. Cake had often provoked similar heart burn. Water gave him temporary relief, but one hour later, the heart burn was followed by cramps in the lower substernal and right hypochondriac regions, which lasted until he took sodium bicarbonate, about ten minutes. He slept that night, suffering no nocturnal pain, and the next day returned to work. Beginning immediately after the attack, in fact the same evening, as he left his car and began to walk, he noted pain in the lower substernal region, radiating upward under the sternum and compelling him to slow his pace. Some relief was afforded by belching. On walking this symptom persisted.

Physical examination three weeks after this attack revealed a stocky man whose lungs were clear and who had no abnormal abdominal findings. Fluoroscopic study revealed some enlargement of the left ventricle. The heart sounds were dull. A musical systolic murmur was heard over the entire precordium. The blood pressure was 140 systolic and 80 diastolic. The electrocardiogram showed no abnormality except for slight slurring of the QRS.

In case 10 the acute onset of angina pectoris followed the pattern of the previous pain, from ulcer, and therefore masqueraded as a recurrence of that lesion.

CASE 11—A man, S. G., complained of pain low in the epigastrium, beginning at the age of 26 and recurring intermittently for twenty-five years. It occurred three hours after meals and often awakened him at 2 a. m. Roentgen examination at the age of 50 revealed a peptic ulcer. On a diet the pain remitted, and he remained without symptoms of ulcer thereafter. At the age of 58 he first complained of pain in the calves on walking a few blocks, compelling him to halt. Despite the marked reduction in the number of cigarettes which he smoked, these symptoms remained unaltered. At the age of 63, while on a short walk one morning, before breakfast, he experienced epigastric pain without radiation that compelled him to halt. Later in the day the pain recurred as he took another walk. That night he was awakened several hours after retiring by the same nonradiating epigastric pain, lasting ten minutes. During the following week he was awakened every night by similar pain. A few days after he began to take alkali after meals, the nocturnal pain remitted.

He was examined four weeks after the onset of these symptoms. There was no abdominal tenderness. Fluoroscopic study revealed a heart normal in size and configuration. The heart sounds were of good quality, there were no murmurs. The blood pressure was 120 systolic and 70 diastolic. The electrocardiogram showed a diphasic T wave in lead IV. After resting in bed for two weeks he noted that walking one or two blocks would bring on pain under the xiphoid process, radiating upward toward the neck and, on occasions, compelling him to rest. He complained no further of nocturnal pain or of postprandial epigastric pain. The anginal pain now was located either under the lower part of the sternum or under the xiphoid process, whereas a few weeks previously it was epigastric in location. An electrocardiogram taken four weeks after the first one showed further inversion of the T wave in lead IV.

This case history illustrates the original abdominal location of anginal pain in a patient with an old peptic ulcer. Subsequently the anginal pain was confined to the usual coronary pathway.

CASE 12—A man, M. U., beginning in his thirty-second year had had epigastric pain four hours after meals, unrelieved by food and often accompanied with vomiting. At the age of 46 he underwent an operation for gastric ulcer. Following the operation he remained well for six years and then began to have rare recurrences of nausea with vomiting, with remissions, up to the age of 60. Five weeks before he was first seen by us (at the age of 60) he complained of constant pain and stiffness of the left shoulder. Two weeks later, while taking a walk he suddenly experienced pain diffusely throughout the right side of the chest, radiating across the midthoracic region to the epigastrium, which compelled him to halt. He thereupon vomited much saliva and bile-stained gastric contents. This afforded him great relief. He felt well the next day, but two weeks later he suffered a recurrent attack of pain and vomiting, lasting fifteen minutes. In the interval between these attacks there were no symptoms of ulcer, but walking 3 to 4 blocks, especially hurriedly, would provoke pain in the right upper region of the chest, always associated with epigastric pressure and compelling him to rest.

He was a thin, sallow man. The lungs were emphysematous, there was no abdominal tenderness. Fluoroscopic study revealed a heart normal in size and configuration. The heart sounds were of good quality, there were no murmurs. The blood pressure was 120 systolic and 70 diastolic. The electrocardiogram showed slurring of the QRS in all leads, a depressed RT segment and a diphasic T wave in lead IV. During the next months he again experienced pain four hours after meals, immediately relieved by food. The pain was always felt first in the right side of the chest or in the lower substernal area, it then radiated to the epigastrium.

CASE 8—I K, a man aged 58, had known of some degree of hypertension for one year. For eight years he had complained of pain in his calves on walking a few blocks, compelling him to slow his pace. He had not suffered from digestive symptoms in the past. At no time did he experience pain in the chest while walking. If he quickened his pace, pain in the calves was felt. Beginning about six weeks before he came for examination and occurring about every other day, attacks of severe midthoracic pain were experienced chiefly at 3 to 4 p. m. as well as in the hours between midnight and 4 a. m. The pain would radiate to the gums, then to the upper dorsal area and to both upper extremities. The attacks of pain lasted one or two hours and were associated with slight chilliness, but there was no perspiration, dizziness, nausea, vomiting or abdominal pain. During the bouts of pain he had no desire for food. On several occasions sodium bicarbonate afforded relief from the pain by inducing belching. The most severe attack, occurring three days before examination, awakened him from sleep at 4 a. m., and the pain persisted for more than two hours. The relief afforded by sodium bicarbonate was transient, lasting but five minutes.

He was a well built man, weighing 147 pounds (66.5 Kg). There was no abdominal tenderness. Inconstant rales were heard at the bases of both lungs. Fluoroscopic study revealed moderate enlargement of the left ventricle, slight enlargement of the left auricle and moderate general dilatation of the aorta. The first heart sound was dull. A systolic murmur was heard at the apex. The blood pressure measured 130 systolic and 75 diastolic. The electrocardiogram showed slurring of the QRS complex in all leads and large Q waves and diphasic T waves in leads I and IV. The temperature was 98 F by mouth. The sedimentation rate of the red blood cells was 18 mm in seventy minutes.

The patient in case 8 had prodromal symptoms of coronary occlusion for six weeks before the closure finally took place. It is unlikely that postprandial anginal pain is caused solely by the increased work of the heart provoked by digestion. Anginal pain may appear while the patient is still eating, or else during the night after digestion is completed. The immediate cessation of postprandial pain so commonly achieved by the eructation of gas also speaks for a neurogenic reflex mechanism.

#### *Abdominal Localization of Anginal Pain in Patients with Antecedent Peptic Ulcer*

CASE 9—A man, M J C, in 1934, at the age of 35, complained for several months of hunger pains in the upper part of the abdomen, occurring three to four hours after meals and relieved by food. Two years later gastrointestinal fluoroscopic examination apparently showed no ulcer. At this time he complained of right-sided abdominal pain, which was subsequently diagnosed as renal calculus. The right kidney was removed for calculi in 1936. In November 1940, while running to catch a street car, he suddenly experienced a sharp pain high up in the epigastrium. The pain lasted about half a minute and did not radiate. Two days later he noted, for the first time, similar nonradiating epigastric pain on walking a few blocks, particularly marked shortly after meals. He would be compelled to rest. Late in November the epigastric pain recurred, became progressively worse and radiated to the left lower part of the chest and to the left upper extremity, and lasted about twenty-four hours. Subsequently the temperature was elevated to 103 F.

We first saw him six days after this attack. The lungs were clear, the heart was not enlarged to percussion, and the heart sounds were dull, there was no hepatic congestion. Several weeks later fluoroscopic study showed slight enlargement of the left ventricle. The electrocardiogram showed low voltage, with slurring of the QRS in all leads. The T wave in lead I was inverted. In lead IV there was a large Q wave and a deep inverted T wave.

The patient in case 9 had had symptoms of peptic ulcer at the age of 35. When he was 51 years old, anginal pain developed on effort, which was experienced in the epigastrium. During the subsequent coronary thrombosis the initial pain was epigastric but radiated to the precordium and the left arm.

CASE 10—A man, I A, at the age of 25, first noted heart burn in the lower substernal area one-half hour after meals. It was relieved by taking some alkali. The attacks persisted for over twenty years without remission, and during this time he never experienced pain in the abdomen. At the age of 46, for the first time, he experienced nocturnal heart burn, which was relieved by alkali. Roentgen examination was first done at the age of 47 and revealed an irregular duodenal cap, which was diagnosed as a duodenal ulcer. The symptoms were controlled by an appropriate diet. At the age of 49, shortly after eating some cake he suffered

When he was 58 years of age, a renal calculus was passed spontaneously. He continued to have short episodes of pain in the right upper quadrant of the abdomen, occurring three to four hours after meals and relieved by alkali. These symptoms would last a few days at a time and would be followed by long remissions. At the age of 62 he first noted mild pressure in the lower anterior part of the chest on walking up grade, he was not compelled to rest. Shortly after this he was awakened at 2 a. m. by pressure in the lower part of the axilla, radiating to the left pectoral fold and lasting about two hours. Examination at this time disclosed little change. There was some increase in the size of the heart, but the electrocardiogram was normal and unaltered. He was given a modified Sippy diet and alkaline powders and remained well for several months, then symptoms of ulcer recurred. At the same time effort involving the use of the right upper extremity provoked the same epigastric pain, irrespective of the hour. Several months later he had recurrence of intermittent pectoral pain on the left side, occurring as a rule at 10 a. m. and at 4 p. m., intensified by food. At that time he noted that recurrences of postprandial symptoms of both the pectoral and the epigastric type were accompanied by difficulty in walking. During periods of freedom from pain he was able to walk quite freely, as much as 10 blocks, even up grade, whereas during a period of postprandial symptoms, walking 2 or 3 blocks, particularly up grade, provoked bilateral pressure in the lower part of the chest, radiating to the left arm and compelling him to slow his pace.

CASE 15—A man, M. W., had been observed at frequent intervals since 1936, when he was 48 years old. He gave no past history of ulcer or ulcer-like symptoms. In April 1936 he first complained of mild pains in the right upper extremity, lasting for a few minutes at a time and bearing no relation to effort. Two weeks after the onset of this symptom, he experienced pinching pain in the anterior part of the chest and the upper dorsal area, which lasted through the night. The next morning morphine was administered by hypodermic injection and he was ordered to bed for a week. On the ninth day after the attack, physical examination revealed a well built man of good color. The lungs were clear. There was no abdominal tenderness. Fluoroscopic study revealed slight enlargement of the left ventricle. The heart sounds were of good quality. There were no murmurs. The blood pressure was 145 systolic and 85 diastolic. The electrocardiogram showed a shallow inverted T wave in lead I. During the remainder of the year 1936 he remained relatively well, suffering only mild pain and slight limitation of motion in the right and then in the left shoulder. An electrocardiogram taken in December 1936 showed an upright T wave in lead I. The years 1937, 1938 and the first half of 1939 were characterized by freedom from symptoms, he worked freely and experienced no distress at work. In July 1939, after walking a few blocks he complained of pain at the middle of the substernal area, which forced him to halt and rest. The heart sounds were now of good quality, the blood pressure, 140 systolic and 90 diastolic. The electrocardiogram showed no abnormality, the T wave in lead I being not only upright but of normal contour and voltage. An electrocardiogram taken in November 1939 was normal. He complained of pain in the chest only on walking in the morning. In May 1940 he stated that the morning angina was unchanged and that he could walk 8 blocks readily in the afternoon. If he took glyceryl trinitrate before leaving his house, he could walk 8 blocks to the station even in the morning. Physical examination in May 1940 showed no change. The electrocardiogram revealed flattening of the T wave in lead II. In lead IV the T wave was small and inverted. There was no history of an acute or severe attack of pain in the chest. During the following eleven months there was no change in the symptoms. In April 1941 he was awakened one night by severe pain in the middle of the anterior part of the chest, which lasted about an hour and necessitated a hypodermic injection of morphine. He suffered an attack on each of the two succeeding days. He remained in bed four weeks. On examination in May 1941, the heart sounds were of good quality, and the blood pressure was 135 systolic and 80 diastolic. The electrocardiogram disclosed a shallow diphasic T wave in lead I and a more deeply inverted T wave in lead IV. There was no abdominal tenderness. Following this attack, from time to time he experienced lower substernal pain unrelated to effort and recurring about every three to five hours, particularly at 3 a. m., when the pain would awaken him. Glyceryl trinitrate afforded relief from the pain for two hours, then it would recur at 5 to 6 a. m. About four to five hours later, during the daytime, the pain would return and would be equally relieved by glyceryl trinitrate. All the attacks began as a peculiar mild distress localized about the umbilicus and quickly radiated into the substernal area. There was no associated perspiration or sensation of hunger. Walking a few blocks, and also excitement, would now induce the substernal pain directly (unaccompanied by the abdominal component). He differentiated clearly the immediate thoracic pain of effort and excitement and the abdominal-thoracic pain which occurred when he was at rest and at intervals characteristic of pain from peptic ulcer. The symptoms showed no tendency to remission for six months. Then, in November 1941, he made a habit of taking 2 drachms (7.76 Gm.) of

and was at times associated with mild cough or belching. The patient stated that the area just to the right of the middle of the sternum had been his "Achilles' heel" since an attack of influenza in 1918. Subsequently, whenever he suffered any infection of the upper respiratory tract he would feel pain first in this area and on coughing would feel as though the sputum were coming from this same spot. Beginning shortly after the onset of the anginal pain on effort, the slightest excitement or emotional upset would provoke the same pattern of pain, beginning at the right parasternal area, radiating to the epigastrium and associated with belching.

The foregoing case history illustrates the radiation of pain in the chest to the epigastrium, as well as the ulcer-like component of vomiting, during the first episode of angina pectoris. The anginal pain was localized to an area in the right side of the chest sensitized twenty-two years previously by an attack of influenza.

CASE 13—A man, M. C., from his twenty-eighth to his thirtieth year was often awakened from sleep at 2 a. m. by heart burn high in the epigastrium, which was relieved by drinking hot water. At the age of 35 he was awakened one night by epigastric pain which lasted until relieved by alkali and a hypodermic injection after one hour. At the age of 50, six months before coming under our observation and while engaged at his usual work he suddenly experienced pain in the epigastrium and the lower anterior part of the chest and vomited food he had recently eaten. He took sodium bicarbonate and was relieved of pain in about half an hour. During the succeeding five months he made no complaints and suffered neither thoracic nor abdominal pain. Then, one day, while rushing to catch a train he experienced severe pain in both hypochondriac areas, radiating to both arms. A short enforced rest brought relief. Since this episode, walking 2 blocks would provoke epigastric pain radiating to both arms, forcing him to halt. He experienced no pain during his routine work.

Physical examination two weeks after the incident of pain on rushing for a train revealed no abnormality in the abdomen. Fluoroscopic examination revealed a heart of normal size and configuration, there was moderate general dilatation of the aortic arch. The heart sounds were of good quality. A faint systolic murmur was heard at the apex. The blood pressure was 100 systolic and 70 diastolic. The electrocardiogram was normal. For the next eight months symptoms were mild and consisted of infrequent pain high in the epigastrium, occurring one-half to one hour after meals as well as on walking 3 to 4 blocks. Then, while at work, at 2 p. m., one-half hour after a light lunch he experienced sudden epigastric pain radiating to the entire anterior part of the chest and to both upper extremities, lasting about ten minutes. Three days later he suffered two recurrences of similar but more severe pain, the first lasting fifteen minutes. The first attack was characterized by epigastric pain alone and lasted twelve hours. Since this episode, walking as little as 50 feet (15 meters) would provoke the epigastric pain radiating to both upper extremities, compelling him to rest, with quick relief. Glyceryl trinitrate relieved the pain. Physical examination now revealed a palpable, slightly tender liver and dulness of the heart sounds. There were alterations in the electrocardiogram, with Q waves and inverted T waves in leads II and III, and evidences of recent infarction of the posterior aspect of the left ventricle. During a four week period of rest at home he suffered no pain, but on leaving home and walking 1 or 2 blocks he experienced the same pressure pain, high up in the epigastrium, compelling him to rest. Glyceryl trinitrate again was effective in abolishing the pain.

The development of progressive myocardial damage with ultimate cardiac infarction, with pain experienced chiefly in the epigastrium, and the subsequent development of "abdominal" angina are well exemplified in the foregoing instance.

*Ready Induction of Angina Pectoris During Periods of Pain from Peptic Ulcer, Less Ready Induction or Entire Remission of Anginal Pain as the Symptoms of Ulcer Are Brought Under Control by Diet and Medication*

CASE 14—A man, H. R., at the age of 36 first experienced epigastric pain about one and a half hours after meals. Peptic ulcer was diagnosed, and he was operated on at the age of 45. Postoperatively he remained well until the age of 51, when similar epigastric pain returned. Two years later, at the age of 53, roentgen examination showed a recurrent ulcer. At the age of 54 he complained of dyspnea on walking a few blocks and of weakness and epigastric pain during work. Physical examination at this time disclosed a well built man of good color, with slight emphysema of the lungs. Fluoroscopic study revealed slight enlargement of the left ventricle. The heart sounds were of good quality, there were no murmurs. The blood pressure was 160 systolic and 80 diastolic. The electrocardiogram was normal.



# PROTECTIVE ACTION OF VITAMIN C AGAINST EXPERIMENTAL HEPATIC DAMAGE

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An associate and I<sup>1</sup> previously found that if a hepatoxin, carbon tetrachloride, were given to dogs they could be made to excrete all instead of about half of a given dose of the sympathomimetic amine amphetamine. More recently I showed that if dogs were put on a maintenance dose of the amine, saturating the animals with vitamin C (ascorbic acid) would reduce the excretion of amphetamine to about one third of the amount normally excreted<sup>2</sup>. This together with the in vitro deamination of the amine demonstrated the role of ascorbic acid in the detoxication of these compounds. However, to our surprise, if dogs saturated with vitamin C were given carbon tetrachloride orally, the excretion of amphetamine did not rise above normal.

These observations suggested that ascorbic acid might protect the animals against the toxic action of carbon tetrachloride on the liver. It was deemed more suitable to turn to guinea pigs for the pursuit of the problem. The purpose of this study, then, has been to determine whether ascorbic acid administered to a group of guinea pigs maintained on a scorbutogenic diet would protect them against hepatic damage.

## PROCEDURE

All the animals were maintained on a diet of Purina mixed rabbit chow checkers,<sup>3</sup> which is quite adequate except for vitamin C. In some instances the pellets of food were ground and mixed with 5 per cent brewers' yeast to supplement the vitamin B complex without influencing the results. Ecker and Pillemer<sup>4</sup> have reported that guinea pigs maintained on a similar diet showed signs of scurvy in twenty-one days and that 10 to 20 mg of ascorbic acid per day was necessary to maintain maximal plasma concentration of the vitamin. Throughout the experiments the animals receiving ascorbic acid were given 30 mg daily. This was made up with half its weight of sodium bicarbonate, dissolved in an equivalent of 1 cc of distilled water and injected subcutaneously immediately.

Hydrazine sulfate was selected for the experimental production of hepatic damage, for Wells<sup>5</sup> has shown that it is a poison with an almost specific effect on the cytoplasm of the parenchymatous cells of the liver. When this chemical is given, the liver alone evidences structural alterations. The substance attacks the cytoplasm primarily, only much later affecting the nucleus, and causes profound fatty degeneration. The urinary products of dogs seem quite normal after a 50 mg per kilogram dose of hydrazine sulfate, according to Underhill and Kleiner<sup>6</sup>.

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From the Department of Physiology, University of Wisconsin Medical School

1 Beyer, K H, and Skinner, J T. The Detoxication and Excretion of Beta Phenylisopropylamine (Benzedrine), *J Pharmacol & Exper Therap* **68** 419 (April) 1940

2 Beyer, K H. The Action of Vitamin C and Phenol Oxidase in the Inactivation of Beta Phenylisopropylamine, *J Pharmacol & Exper Therap* **71** 394 (April) 1941

3 The composition of the diet was as follows: protein, 15.35 per cent, fat, 2.38 per cent, carbohydrates, 64.61 per cent (including 16.86 per cent fiber), calcium carbonate, phosphorus, sodium chloride, potassium iodide, magnesium sulfate, and per pound (0.5 Kg) approximately 5,000 international units of vitamin A, approximately 400 international units of vitamin B<sub>1</sub>, approximately 3,000 micrograms of riboflavin (vitamin B<sub>2</sub>) and negligible vitamin C.

4 Ecker, E E, and Pillemer, L. Vitamin C Requirement of the Guinea Pig, *Proc Soc Exper Biol & Med* **44** 262 (May) 1940

5 Wells, H G. The Pathological Anatomy of Hydrazine Poisoning, *J Exper Med* **10** 457 (July) 1908

6 Underhill, F P, and Kleiner, J S. The Influence of Hydrazine upon Intermediary Metabolism in the Dog, *J Biol Chem* **4** 165 (Feb) 1908



magnesium hydroxide at 8 30 p m, one-half hour before retiring Within a few days he noted that the nocturnal attacks, though of the same frequency, were of lesser intensity In general, the attacks at rest were modified and milder while he was taking erythrol tetranitrate, from August to November 1941

Examination in November 1941 showed minor electrocardiographic alterations but no other changes There was no abdominal tenderness He was now given a modified Sippy diet and aluminum hydroxide gel after meals Three weeks later he reported that he felt stronger and better generally Attacks of thoracic pain continued to appear at 10 a m, 3 p m and 3 to 4 a m, rarely at 7 p m, but were distinctly milder and quickly relieved by glyceryl trinitrate No change was noted on examination In addition to these drugs, atropine  $\frac{1}{150}$  grain (0.43 mg) and phenobarbital  $\frac{1}{2}$  grain (0.032 Gm), each three times daily, were prescribed He was last seen in January 1942 Improvement was continuous About once a week he was awakened at 2 to 4 a m by the same pressure in the lower substernal area, quickly relieved by glyceryl trinitrate Rarely he experienced the pain at 3 to 4 p m, when glyceryl trinitrate also brought quick relief He had taken a capsule containing  $\frac{1}{150}$  grain of atropine and  $\frac{1}{2}$  grain of phenobarbital regularly He took an alkali rarely, having found that the greatest relief was obtained from the capsule alone Physical examination showed no significant change

CASE 16—A man, H B, began at the age of 46 to complain of intermittent pain in the left arm, unrelated to exertion Two years later, while he was walking, there was a sudden onset of squeezing apical pain radiating into the left arm and compelling him to rest This pain persisted on walking

He was a thin man There were healed scars at the apexes of both lungs Fluoroscopic study revealed a heart of normal size and configuration The sounds were of good quality, and there were no murmurs The blood pressure was 110 systolic and 70 diastolic The electrocardiogram showed a flat T wave in lead I, a shallow T wave in leads II and III and an inverted T wave in lead IV

At the age of 52 he complained of midabdominal pain occurring, as a rule, two to three hours after meals and relieved by food The pain was not felt during the night Roentgen examination shortly after this symptom appeared revealed no ulcer Frequently with the midabdominal pain he experienced severe pain in the lower substernal and subxiphoid regions The pain would be so severe and compelling as to force him to eat something for relief He was given a modified Sippy diet, a colloidal suspension of aluminum hydroxide and atropine Two months later he reported that after he began taking these medicines the hunger pains which occurred two hours after meals remitted and that he walked more freely as much as 5 blocks Formerly he had been able to walk at best 1 or 2 blocks, then he would be stopped by abdominal distention radiating into the lower part of the chest as pain An electrocardiogram taken at this time showed some change The T wave in lead I was upright but of low voltage, it was diphasic in lead IV

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on the vitamin C-deficient diet for sixteen days and then killed, and their livers were examined and analyzed. Grossly, these livers were no different from those of normal guinea pigs. If one expresses the relation as percentage of body weight, the livers from deficient and from normal guinea pigs were similar. On the basis of these data the livers of vitamin C-deficient animals tended to have a higher lipid content than did those of animals on an adequate diet, but the difference was not significant, especially since only 7 of the 18 vitamin C-deficient animals had a

TABLE 2—*Analysis of Livers from Guinea Pigs Given Injections of Ascorbic Acid*

Number of Guinea Pig	Washed Liver, Percentage of Body Weight	Dry Matter, Percentage of Total Weight of Liver	Fat, Percentage of Dry Matter of Liver
H 1	3.9	28.4	9.8
H 2	5.0	24.3	9.9
H 3	4.0	28.8	11.1
H 4	3.7	28.8	11.1
H 5	5.3	28.3	10.8
H 6	3.9	30.4	10.0
H 7	3.4	30.8	14.0
H 8	3.7	29.5	12.8
H 9	3.7	31.3	11.8
H-10	3.8	25.6	14.0
Average	4.0	28.6	11.5

TABLE 3—*Analysis of Livers from Vitamin C-Deficient Guinea Pigs*

Number of Guinea Pig	Washed Liver, Percentage of Body Weight	Dry Matter, Percentage of Total Weight of Liver	Fat, Percentage of Dry Matter of Liver
D-1	3.2	24.7	10.7
D-2	3.7	28.4	13.0
D-3	3.5	29.1	12.6
D 4	3.6	32.0	14.4
D 5	4.0	29.0	17.4
D-6	5.4	27.8	12.5
D 7	5.1	21.8	11.7
D-8	3.6	23.1	9.9
D-9	4.0	21.5	9.1
D-10	3.8	21.8	9.7
D-11	4.0	25.0	12.4
D-12	4.0	27.6	15.5
D 13	4.6	22.0	13.9
D 14	3.8	23.7	14.5
D 15	4.2	26.1	12.9
D 16	4.0	23.1	11.2
D-17	3.8	22.8	12.1
D-18	4.3	25.2	12.4
Average	4.0	25.3	12.5

lipoid content above the average of 12.5 per cent for that group (table 3). On the other hand, since vitamin C deficiency does markedly impair hepatic function, one cannot entirely dismiss this slight increase.

*Vitamin C and Hepatic Damage*—Having found that there is really little difference histologically or in fat content between the livers of guinea pigs that have been maintained on an adequate diet and those maintained on a vitamin C-deficient diet with or without injections of ascorbic acid, I could then examine my original hypothesis—that vitamin C protects against hepatic damage. The experiments were set up as described in the preceding section. Briefly, two groups of guinea pigs were maintained on a diet deficient in vitamin C, and one group (A)

The experiment was set up as follows. For purposes of comparison it was necessary to know the percentage of lipid in the livers of normal guinea pigs, of ones rendered deficient in vitamin C and of ones given an injection of 30 mg of ascorbic acid per day. This was to determine whether low or high intake of the vitamin influenced the lipid content of the liver. To determine whether vitamin C protected the animals against hepatic damage caused by hydrazine other guinea pigs weighing between 250 and 400 Gm were divided into two groups of 6 or more each. Both groups were placed on the vitamin C-deficient diet, and their gain in weight was followed every other day. One group (A) received 30 mg of ascorbic acid subcutaneously daily. The other group (B) did not receive injections of the vitamin. At first the gain in weight in both groups was the same, but later the animals in group A gained more rapidly than did the ones in group B. After about sixteen days the guinea pigs in group B ceased to gain weight. Then the guinea pigs in both groups were given injections of 25 mg of hydrazine sulfate per kilogram of body weight on two successive days. Two days after the second injection of hydrazine the animals were killed and autopsied. The livers were removed from the bodies, examined grossly and in many instances photographed with kodachrome film for future reference. After that, the livers were weighed and a section was preserved for histologic study. A weighed amount of the remainder of each liver was dried in an oven, weighed again and powdered for extraction of the lipid fraction. The lipoids of a weighed amount of liver from each guinea pig were extracted

TABLE 1—*Analysis of Livers from Normal Guinea Pigs*

Number of Guinea Pig	Washed Liver, Percentage of Body Weight	Dry Matter, Percentage of Total Weight of Liver	Fat, Percentage of Dry Matter of Liver
N 1	4.2	32.8	9.1
N 2	4.1	36.2	9.7
N 3	3.8	31.2	9.9
N 4	3.8	30.5	8.0
N 5	3.5	30.7	9.3
N 6	3.9	32.3	11.0
N 7	3.7	30.0	13.5
N 8	3.6	28.0	14.0
N 9	3.2	28.3	12.3
N 10	4.3	32.3	11.9
N 11	2.7	45.0	8.8
N 12	4.0	38.8	7.5
N 13	4.7	30.2	9.2
N 14	4.9	29.6	9.1
Average	3.9	32.5	10.2

with chloroform in a modified Soxhlet continuous extractor, the period of extraction being twenty-four hours, and at least two determinations were made on each sample of liver. After extraction the chloroform was allowed to evaporate from the lipid fraction at 80 to 90 F, the residue was weighed and calculated as a percentage of the dry weight of liver. Thus anatomic and chemical evidence of any damage done to the livers was obtained.

## RESULTS

*Analysis of Normal Livers*—The results of analysis of the livers of 10 normal guinea pigs are given in table 1. The washed livers removed from the bodies of normal guinea pigs represented an average of 3.9 per cent of the body weight, the dry matter 32.5 per cent of the total liver weight and the lipoids 10.2 per cent of the dry matter. Control values for livers from 10 guinea pigs receiving 30 mg of ascorbic acid subcutaneously for sixteen days are given in table 2. Comparing tables 1 and 2, one can see that the data in the latter table agree remarkably closely with those for the normal guinea pigs.

In an effort to help clear up an uncertainty<sup>7</sup> about the effect of avitaminosis C on hepatic fat and for comparison with other data, 18 guinea pigs were maintained

<sup>7</sup> Spellberg, M. A., and Keeton, R. W. Production of Fatty Livers in Guinea Pigs with Scorbutogenic Diets, *Proc Soc Exptl Biol & Med* **41** 570 (June) 1939.

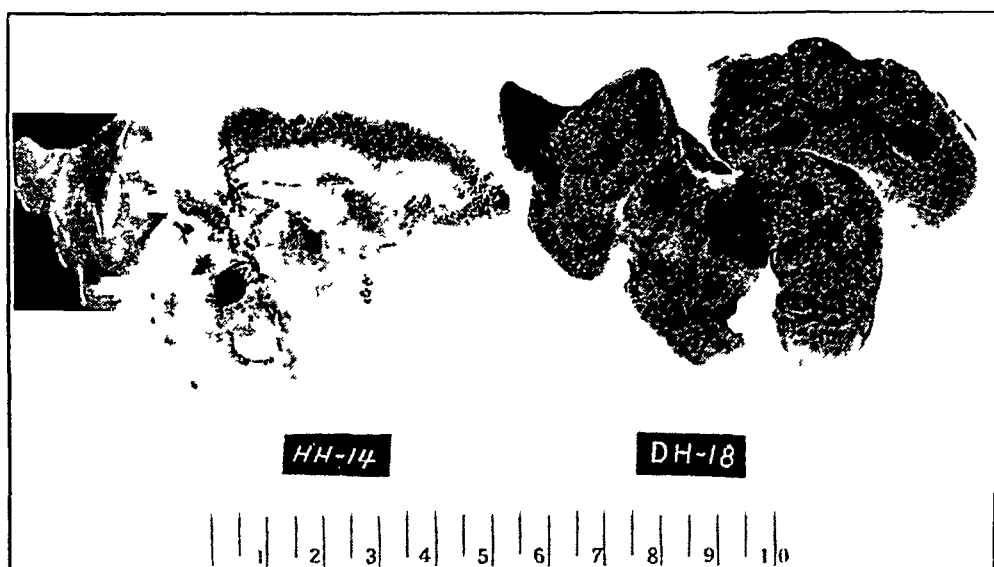


Fig 1—The effect of hydrazine on the livers of guinea pigs. Guinea pig HH-14 had received subcutaneous injections of 30 mg of ascorbic acid per day. Guinea pig DH-18 had not received vitamin C. Both animals were on a scorbutogenic diet for sixteen days before being given hydrazine sulfate, 25 mg per kilogram on two successive days. Expressed as percentage of total body weight, the liver of guinea pig DH-18 was 68 per cent heavier than that of guinea pig HH-14.

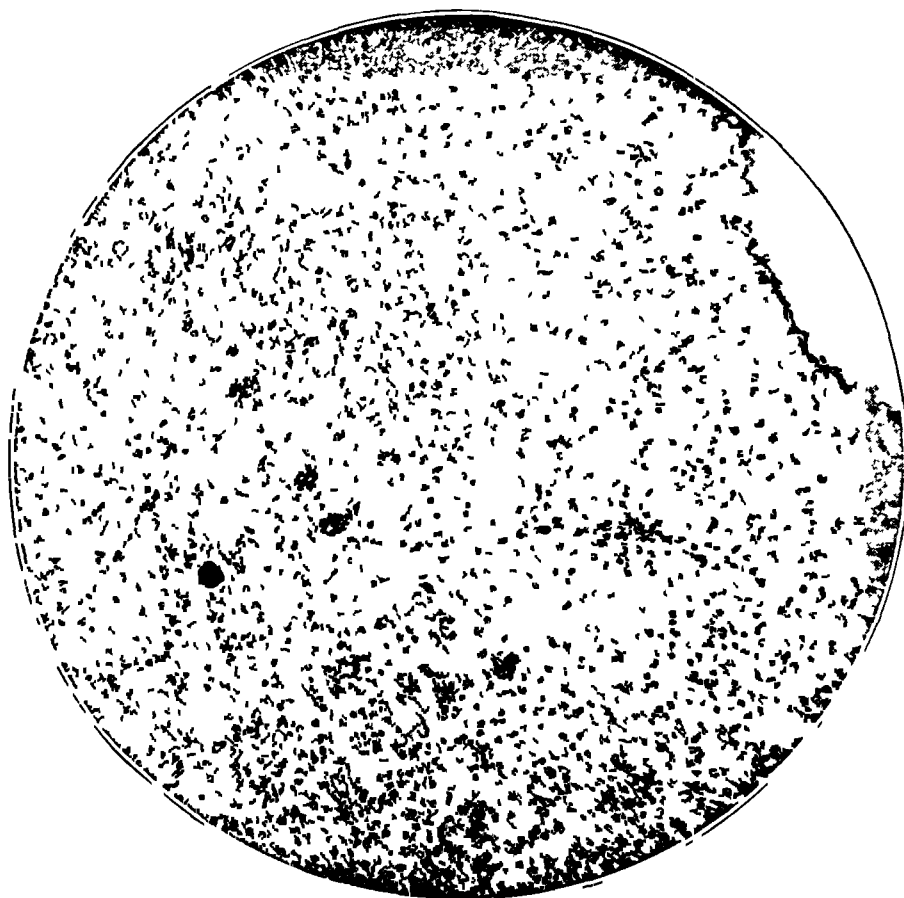


Fig 2—A section from the liver of guinea pig HH-14,  $\times 100$ , stained with hematoxylin and eosin. This section was selected to show one lobule with the central degeneration typical of hydrazine poisoning. The architecture around the smaller central vein is more typical of the animals that have received adequate vitamin C.

was given daily injections of ascorbic acid Guinea pigs in both groups received hydrazine on the same days after those in group B ceased to gain weight

Table 4 presents data on 19 vitamin C-deficient guinea pigs, each of which was given a total of 50 mg of hydrazine sulfate per kilogram of body weight

TABLE 4—*Analysis of Livers from Vitamin C-Deficient Guinea Pigs Given Injections of Hydrazine*

Number of Guinea Pig	Washed Liver, Percentage of Body Weight	Dry Matter, Percentage of Total Weight of Liver	Fat, Percentage of Dry Matter of Liver
DH 1	10.2	14.8	20.0
DH 2	5.0	29.4	16.2
DH 3	5.5	19.3	22.6
DH 4	5.3	26.4	27.5
DH 5	6.4	23.5	19.0
DH 6	5.7	24.0	19.8
DH 7	1.3	26.8	18.9
DH 8	4.4	26.0	20.0
DH 9	4.0	24.5	17.4
DH 10	5.9	26.6	25.8
DH 11	5.2	22.3	29.8
DH 12	7.1	21.8	30.0
DH 13	5.5	25.7	23.2
DH 14	5.1	21.4	20.5
DH 15	4.7	26.6	24.3
DH 16	5.3	23.7	17.0
DH 17	5.3	22.0	24.0
DH 18	4.5	29.6	34.2
DH 19	4.9	29.0	31.8
Average	5.5	24.4	23.3

TABLE 5—*Analysis of Livers from Guinea Pigs Given Both Vitamin C and Hydrazine*

Number of Guinea Pig	Washed Liver, Percentage of Body Weight	Dry Matter, Percentage of Total Weight of Liver	Fat, Percentage of Dry Matter of Liver
HH 1	5.5	25.0	15.5
HH 2	4.8	24.5	16.7
HH 3	4.8	27.6	18.5
HH 4	4.7	27.2	14.8
HH 5	5.6	22.0	15.8
HH 6	4.0	21.3	14.2
HH 7	4.2	21.5	15.9
HH 8	4.2	21.9	15.2
HH 9	5.0	19.0	12.0
HH 10	4.0	23.3	16.3
HH 11	3.3	22.3	15.2
HH 12	4.5	20.8	12.1
HH 13	3.8	28.2	17.8
HH 14	4.4	23.0	16.2
HH 15	4.7	19.5	14.7
HH 16	5.5	23.0	14.8
HH 17	4.2	22.5	15.4
HH 18	4.1	29.6	14.3
Average	4.5	23.4	15.5

subcutaneously Compared to the vitamin C-deficient animals in table 3, there was a 37.5 per cent increase in the liver weight as compared to body weight in the case of the animals rendered toxic The figures for percentage of water and dry matter are almost identical in the two sets of data One has only to compare the lipid content of the two groups of animals to visualize the fatty nature of the livers of the animals receiving hydrazine There was an 86.5 per cent increase

its liver weighed 20.6 Gm. The paleness of the liver of guinea pig DH-18 as compared with that of guinea pig HH-14 is evident. Actually, the former liver was quite yellow.

Microscopically, it is in the livers of guinea pigs having received ascorbic acid that the early stages in the pathogenesis of this fatty degeneration due to hydrazine can be traced best. Here one sees that the process begins at the center of the lobule, decreasing in severity as it spreads toward the periphery. The process begins as a cloudy swelling of the cytoplasm. As the degeneration develops, one sees areas of condensation and rarefaction in the cytoplasm, as manifested by staining reactions, cell demarcation becomes indistinct, and the architecture of

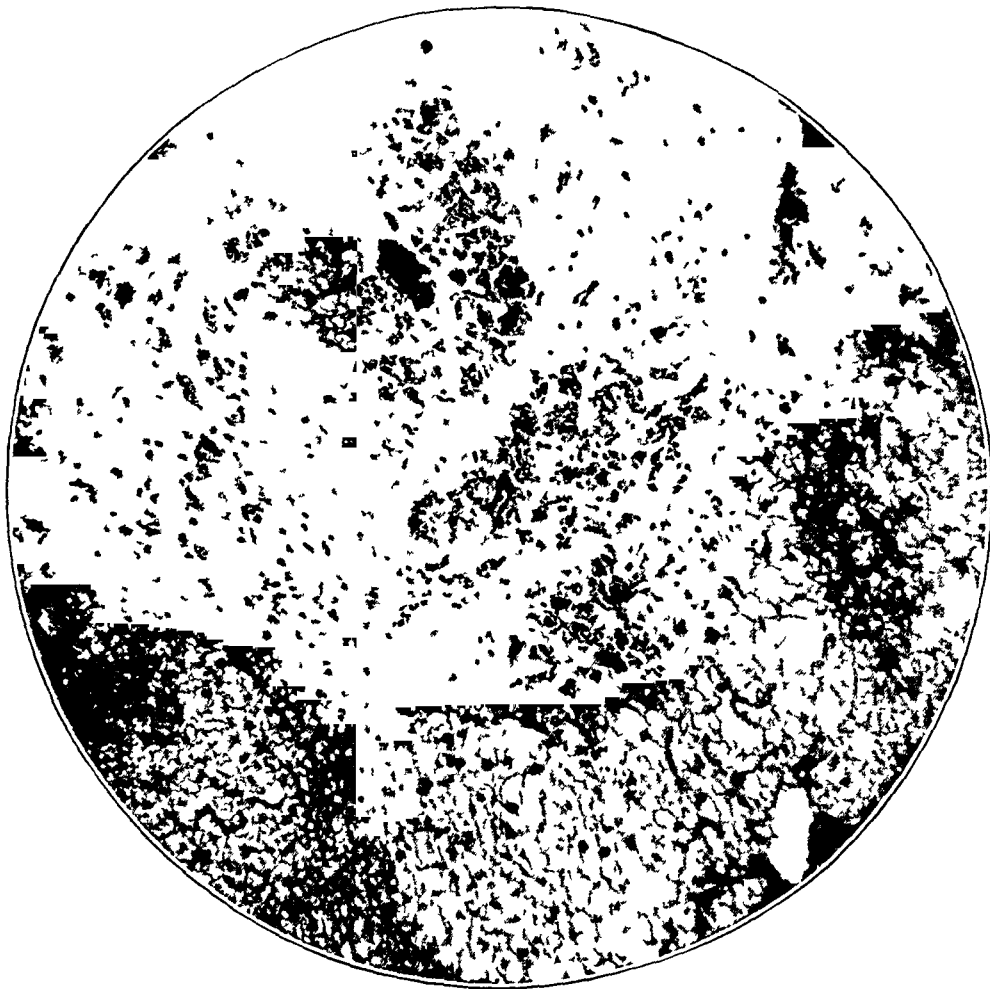


Fig. 4—A section from the liver of vitamin C-deficient guinea pig DH-19 which had been damaged by hydrazine,  $\times 100$ , stained with hematoxylin and eosin. Though the magnification is the same as that of figure 2, the increase in the size of cells, the general loss of architecture and the destruction of cells and nuclei involved in the fatty necrosis are obvious. Both this liver and that represented in figures 2 and 3 had lipid contents approximating the average for the respective experimental groups.

the lobule becomes increasingly distorted. Finally, one may see isolated cells containing vacuoles in the cytoplasm, presumptive evidence of the presence of fat at one time. Manifestation of nuclear involvement is not apparent until relatively late in the process, and then it is one of early karyolysis. This is seldom seen in the livers of animals receiving adequate amounts of vitamin C.

Figures 2 and 3 show a section from the liver of guinea pig HH-14 at two different magnifications. The section under low power (fig. 2) has been deliberately selected to show the central involvement of the lobule typical of the patho-

in the lipoid content of the livers of vitamin C-deficient animals that received hydrazine over that of the control avitaminotic animals

Hydrazine did increase the lipoid content of the liver in animals that received an adequate amount of vitamin C (table 5), as compared with the controls given injections of the vitamin (table 2). There was no significant increase in the weight of these livers, though the percentage of dry matter was decreased 18.2, which suggests the hydropic changes verified by histologic examination.

Finally a comparison of tables 4 and 5 is of interest. As a result of the hydrazine poisoning those animals that did not receive an adequate amount of vitamin C showed a 22.2 per cent greater liver weight and a 50.3 per cent greater lipoid content of their livers than did the guinea pigs that received ascorbic acid.

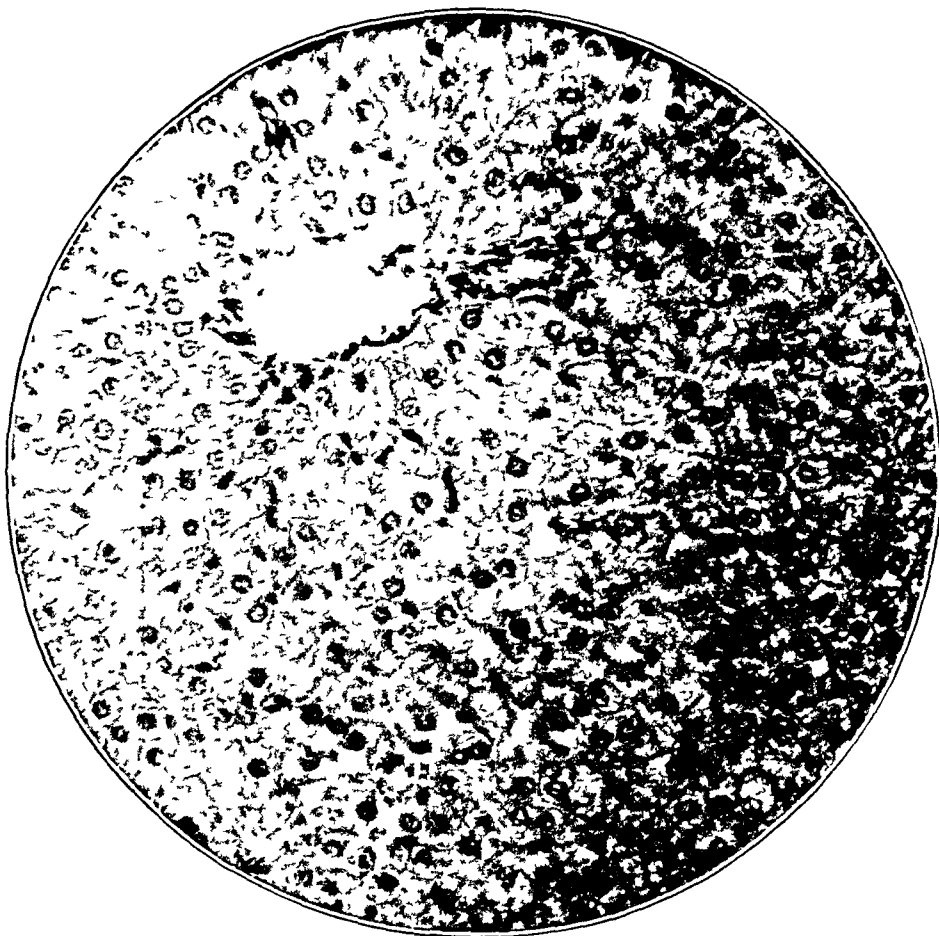


Fig 3—A portion of the section shown in figure 2,  $\times 400$ . The cellular appearance is essentially normal. There are some hydropic changes in the cytoplasm.

*Gross and Microscopic Evidence*—These analytic findings are borne out both by gross and by microscopic evidence.

Grossly, the livers of animals that received vitamin C and hydrazine were almost indistinguishable from the livers of normal guinea pigs. The livers of the guinea pigs deficient in vitamin C and given injections of hydrazine were relatively large, pale to definitely yellow, friable, somewhat hemorrhagic and yellowish on cut surfaces. Figure 1 compares the livers from 2 guinea pigs. Both animals were given injections of hydrazine, but guinea pig HH-14 received vitamin C and guinea pig DH-18 did not. The difference in size is not so apparent unless one appreciates the difference in weight of the 2 animals. Guinea pig HH-14 weighed 430 Gm, and its liver weighed 19.1 Gm. Guinea pig DH-18 weighed 290 Gm, and

him to suggest that dextrose might be beneficial in the prevention and treatment of hepatic necrosis induced by chloroform anesthesia. While the use of this form of therapy has had wide acceptance, the actual explanation of how it works is not yet clear. Recently it has been suggested that a diet emphasizing protein and carbohydrate may be better than one of carbohydrate alone.<sup>10</sup>

There is increasing evidence that ascorbic acid plays a significant role in the metabolism of proteins and carbohydrates in the liver, as well as in detoxication and the healing of wounds. Miwa<sup>11</sup> showed that in experimental scurvy the Golgi apparatus was decreased, but if ascorbic acid was given both the vitamin C level and the Golgi apparatus increased in the liver and the kidney. Also, the number of Golgi apparatus nearly paralleled the content of vitamin C in the damaged livers of rabbits. Murakami<sup>12</sup> found that feeding guinea pigs on a vitamin C-deficient diet decreased the excretion of bile and of bile pigment together with the detoxicating functions of the liver. If ascorbic acid was given to the animals, the disturbance in these functions was removed. In view of the present understanding of the function of the Golgi apparatus, these observations of Miwa and Murakami tend to substantiate each other.

It has been known since 1903 that leucine, tyrosine and aminoacetic acid<sup>13</sup> are eliminated in considerable quantities in the urine after poisoning with the hepatotoxin phosphorus, but only recently evidence has been found for a direct or an indirect participation of vitamin C in protein metabolism. Romanyuk<sup>14</sup> has shown that cathepsin activity of kidney, liver and muscle was increased during avitaminosis C in guinea pigs. Levine, Marples and Gordon<sup>15</sup> reported that some premature infants excreted parahydroxyphenyllactic acid and parahydroxyphenylpyruvic acid. If phenylalanine or tyrosine was fed to the infants, the excretion of the substances just mentioned increased, but if human milk or ascorbic acid was given in the diet, the excretion of the compounds dropped to zero. Similar results were obtained by Sealock and Silberstein,<sup>16</sup> who found that vitamin C-deficient guinea pigs fed 0.5 Gm or more of tyrosine per day excreted homogentisic acid, parahydroxyphenylpyruvic acid and parahydroxyphenyllactic acid. If 10 mg or so of ascorbic acid was fed daily to the animals, the excretion of these metabolites was prevented.

10 (a) Miller, L. L., and Whipple, G. H. Chloroform Liver Injury Increases as Protein Stores Decrease. Studies in Nitrogen Metabolism in These Dogs, *Am J M Sc* **199** 204 (Feb) 1940. (b) Messinger, W. J., and Hawkins, W. B. Arsphenamine Liver Injury Modified by Diet. Protein and Carbohydrate Protective, but Fat Injurious, *ibid* **199** 216 (Feb) 1940. (c) Ravdin, I. S. The Protection of the Liver from Injury, *Surgery* **8** 204 (Aug) 1940.

11 Miwa, A. Golgi's Apparatus and Vitamin C. Experimental Studies, *Orient J Dis Infants* **26** 3 (July) 1939.

12 Murakami, O. The Influence of Ascorbic Acid upon the Liver Function and the Mutual Relation Between Vitamins B and C. I. Influence of Ascorbic Acid upon the Pigment Excreting Function of the Liver, *Jap J Gastroenterol* **11** 1 (July) 1939.

13 Abderhalden, E., and Bergell, P. Concerning the Elimination of Monoaminoacids in the Urine of Dogs Following Phosphorus Poisoning, *Ztschr f physiol Chem* **39** 464, 1903.

14 Romanyuk, N. M. Cathepsin Activity in the Brain and Muscles During C Avitaminosis, *Biochem J (Ukraine)* **14** 354, 1940.

15 Levine, S. Z., Marples, E., and Gordon, H. H. Defect in the Metabolism of Aromatic Amino Acids in Premature Infants. The Role of Vitamin C, *Science* **90** 620 (Dec 29) 1939.

16 Sealock, R. R., and Silberstein, H. E. The Excretion of Homogentisic Acid and Other Tyrosine Metabolites by the Vitamin C Deficient Guinea Pig, *J Biol Chem* **135** 251 (Aug) 1940.



genesis of this process but infrequently advanced to this degree in the livers of guinea pigs that have received vitamin C. The granular, fairly normal appearance of the cytoplasm is evident at the higher magnification (fig. 3).

Examination of sections from livers of vitamin C-deficient guinea pigs that have received hydrazine reveals the final stages in this pathogenesis. Here one sees relatively little of the early stages, for in almost all the lobules there is widespread vacuolation of the swollen cells, some of them containing nuclei having some semblance of normality and others showing only a hematoxylin-stained shell or nuclear membrane. In some lobules the process has gone on to necrosis. In these the remnants of cells are large, containing little or no cytoplasmic material.

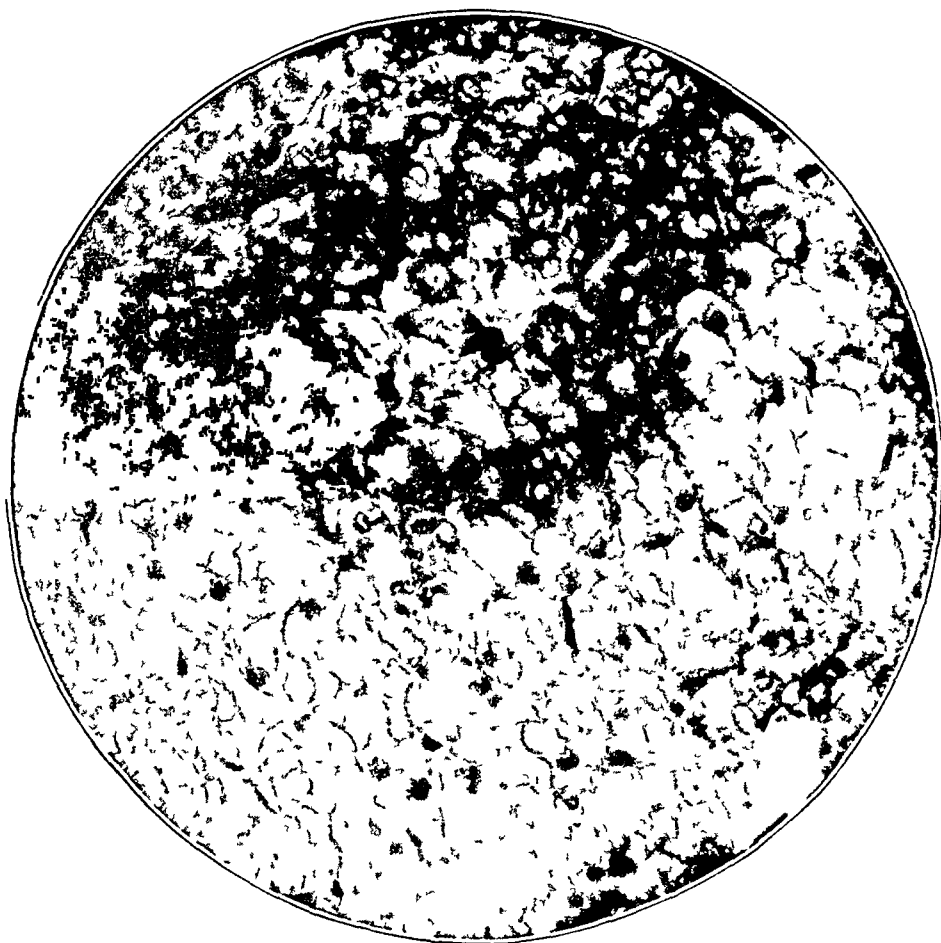


Fig 5—A portion of the section shown in figure 4,  $\times 400$

and sometimes no evidence of a nucleus. These later developments are to be seen in figures 4 and 5, the magnifications of which are the same as those of figures 2 and 3, respectively.

#### COMMENT

It is not to be suggested that ascorbic acid supplant the use of dextrose in the treatment of acute and subacute hepatic damage. Rather, it would seem that the two substances used together would be more efficacious than either alone. There is evidence for such a viewpoint.

Beddard,<sup>8</sup> in 1908, was probably the first to report the use of carbohydrate in the treatment of a hepatic disease, though the work of Rosenfeld<sup>9</sup> also led

<sup>8</sup> Beddard, A. P. A Suggestion for Treatment in Delayed Chloroform Poisoning, *Lancet* 1 782 (March 14) 1908.

<sup>9</sup> Rosenfeld, G. Fat Synthesis. Part II, *Ergebn d Physiol* 2 50, 1903.

# THE HEART IN PULMONARY EMBOLISM

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Theophilus Bonetus in his *Sepulchretum* in 1679 is reported by White<sup>1</sup> to have recorded cases of dyspnea, rapid breathing and blood spitting which presumably were due to pulmonary embolism and pulmonary infarction. However, it remained for Virchow,<sup>2</sup> the creator of the doctrine of embolism and thrombosis, in 1856, to record an early case in which embolism of the pulmonary arteries was described as the cause of sudden death. It is of interest to note in this report by Virchow that mention is made of the mechanism of death in pulmonary embolism. He attributed death primarily to failure of the heart as a result of a decrease of flow through the coronary arteries and stated that at necropsy the heart usually was found in the state of diastole.

More recently the mechanism of death in pulmonary embolism has been studied in experimental animals in an endeavor to determine the relative importance of mechanical and reflex factors. Dunn,<sup>3</sup> in 1920, reported the effect of injecting starch particles into the veins of goats. The particles lodged in the pulmonary arterioles, and death followed in five minutes to eight hours, depending on the amount of starch used. Dunn noted a rise of venous pressure, a drop of arterial pressure and an increase of respiratory rate. Section of the vagus nerve largely abolished the tachypnea, which could be reproduced again by electric stimulation of the central end of the nerve. This work was repeated by de Takáts, Beck and Fenn<sup>4</sup> in 1939, with similar results.

In 1923 Haggart and Walker<sup>5</sup> reported on quantitative closure of the pulmonary artery in cats and the effect on the functioning of the systemic circulation. It was noted that clamping of the left branch of the pulmonary artery increased the pulmonary arterial pressure 29 per cent without changing the systemic arterial pressure, the cardiac size or the cardiac output. The respiratory rate, however, increased 25 per cent. By slowly constricting the main pulmonary artery, Haggart and Walker found that about 60 per cent of the lumen could be occluded before a significant variation in the systemic circulation occurred. When more than 85 per cent of the

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This article is an abridgment of a thesis submitted by Dr. Currens to the Faculty of the Graduate School of the University of Minnesota in partial fulfillment of the requirements for the degree of Master of Science in Medicine.

1 White, P. D. Pulmonary Embolism and Heart Disease. A Review of Twenty Years of Personal Experience, *Am J M Sc* **200**:577-581 (Nov) 1940.

2 Virchow, R. Neuer Fall von todlicher Embolie der Lungenarterien, *Virchows Arch f path Anat* **10**:225-228, 1856.

3 Dunn, J. S. The Effects of Multiple Embolism of Pulmonary Arterioles, *Quart J Med* **13**:129-147 (Jan) 1920.

4 de Takáts, G., Beck, W. C., and Fenn, G. K. Pulmonary Embolism. An Experimental and Clinical Study, *Surgery* **6**:339-367 (Sept) 1939.

5 Haggart, G. E., and Walker, A. M. The Physiology of Pulmonary Embolism as Disclosed by Quantitative Occlusion of the Pulmonary Artery, *Arch Surg* **6**:764-783 (May) 1923.

Since 1865 it has been repeatedly shown that in hepatic damage by hepatotoxins the glycogen content of the liver is rapidly and almost completely exhausted<sup>17</sup>. An interesting isolated observation was made by Ratsimamanga,<sup>18</sup> namely, that in guinea pigs maintained on a vitamin C-deficient diet liver glycogen and muscle glycogen decreased to one fifth of normal and phosphocreatine fell to one third of normal, while muscle lactate and blood lactate tended to increase. The reports of Watanabe,<sup>19</sup> Morelli and d'Ambrosio<sup>20</sup> and Terada<sup>21</sup> are in agreement that ascorbic acid injected into guinea pigs or rabbits increased the glycogen content of the liver. According to Watanabe, vitamin A and vitamin D had no effect and vitamin B<sub>1</sub> and vitamin B<sub>2</sub> had but slight effect on glycogen production. Hjorth<sup>22</sup> and Dienst<sup>23</sup> found that administration of vitamin C increased the dextrose tolerance of normal and of vitamin C-deficient patients. Fan and Woo<sup>24</sup> and Vasile and Pecorella<sup>25</sup> observed that in children with glycogen disease and creatinuria there was a disappearance of creatine and an increase in the excretion of creatinine in the urine if 200 mg of ascorbic acid was fed daily. This Vasile and Pecorella attributed to an increased utilization of carbohydrate in the presence of the vitamin, resulting in an increased accumulation of glycogen in the tissues.

Since on the basis of existing evidence vitamin C does play a part in the intermediate metabolism of proteins and is necessary for the presence of Golgi apparatus and production of bile and its pigments and since its absence or presence results in a diminution or increase in the glycogen content of the liver with a decrease or increase in dextrose tolerance, it seems a definite factor in the maintenance and repair of hepatic function and structure. The experiments presented in this communication seem to bear out the theory that vitamin C does protect against hepatic damage.

#### SUMMARY

Analytic and histologic evidence is presented for the protective action of vitamin C against hepatic damage. Vitamin C-deficient guinea pigs showed an average of 50.3 per cent more fat in their livers than did guinea pigs receiving adequate ascorbic acid when both groups receiving the same diet were given the hepatotoxin hydrazine. Gross and microscopic evidence bore out the severity of the fatty degeneration in the vitamin C-deficient animals and the relatively mild involvement of the livers of normal guinea pigs receiving the compound.

While glycogen replacement therapy has met with the accord of time, carbohydrate utilization and glycogen storage, as well as intermediary metabolism of protein, are at least in part dependent on an adequate body content of ascorbic acid.

426 North Charter Street

17 Saikowsky. Concerning the Fatty Metamorphosis of the Organs Following the Internal Use of Arsenic, Antimony and Phosphorus, *Virchows Arch f path Anat* **34** 73, 1865.

18 Ratsimamanga, A. R. The Influence of Ascorbic Acid on the Behavior of the Organism at Rest, *Travail humain* **1** 303, 1939.

19 Watanabe, I. Effect of Various Vitamins on Glycogen Content of Experimentally Damaged Liver, *Tohoku J Exper Med* **35** 65 (Jan) 1939.

20 Morelli, A., and d'Ambrosio, L. Ascorbic Acid and Liver Glycogen, *Arch di sc biol* **24** 351 (Aug) 1938.

21 Terada, K. Effect of Vitamin C and Related Substances upon Glycogen Metabolism, *Tohoku J Exper Med* **36** 180 (July) 1939.

22 Hjorth, P. The Influence of Vitamin C on Carbohydrate Metabolism, *Acta med Scandinav* **105** 67, 1940.

23 Dienst, C. Action of Vitamins B and C in Diabetes, *Deutsche med Wchnschr* **65** 710 (May 5) 1939.

24 Fan, C., and Woo, T. T. Effect of Vitamin C on Creatine and Creatinine Metabolism, *Proc Soc Exper Biol & Med* **45** 90 (Oct) 1940.

25 Vasile, B., and Pecorella, F. The Influence of Vitamins on the Metabolism of Creatin Substances in Childhood. I. The Effect of Vitamin C, *Pediatrics* **47** 130 (Feb) 1939.

and de Takáts<sup>10</sup> recently presented experimental evidence which strongly supports the value of papaverine in overcoming the constriction of the pulmonary arterial tree in pulmonary embolism. Likewise they found that powerful bronchial constriction occurs in dogs and that this often is abolished by atropine in sufficient doses and, to a less extent, by papaverine.<sup>11</sup>

The possibility of a pulmonocoronary reflex has been postulated by Scheif and Schonbrunner,<sup>12</sup> who demonstrated electrocardiographic changes in 2 of 10 dogs in which pulmonary embolism was produced. The changes in the electrocardiogram were interpreted as evidence of decreased flow through the coronary arteries. As further suggestive evidence of decreased flow through the coronary arteries following pulmonary embolism, they cited 2 cases in which angina pectoris developed after the embolism. The pain in each of these 2 cases was relieved by nitrite.

Indirect evidence of some type of nervous reflex has been presented by de Takáts, Beck and Fenn in the experimental field. Dogs subjected to massive pulmonary embolism died immediately after the embolism in 100 per cent of the experiments. Survival of 68 per cent of animals from ten minutes to twenty-four hours was obtained by immediate intravenous injection of a solution of atropine salt, similar results were obtained in 60 per cent of the animals by the use of papaverine. The action of atropine suggests the abolition of some undesirable vagal reflex, while papaverine acts directly on the smooth muscle of the pulmonary arteries, thus decreasing the strain on the right ventricle.

Experimental attempts to produce death in animals without occlusion of the major portion of the pulmonary artery by emboli have been unsatisfactory. Mann,<sup>13</sup> in 1917, endeavored to produce sudden death in dogs by introducing emboli (paraffin and blood clots) into both anesthetized and unanesthetized animals. He was concerned to find out whether emboli obstructing a relatively small portion of the pulmonary circuit could cause sudden death. The results of all the experiments were the same. In order to produce death or to imperil the life of the animal seriously, he found it imperative to obstruct the pulmonary artery greatly, either with one large embolus or with multiple small emboli. In each instance in which death occurred, necropsy revealed "almost complete" obstruction of the pulmonary circuit. Hall and Ettinger<sup>14</sup> arrived at similar conclusions in 1933 with similar experiments. These authors also attempted to demonstrate a reflex on the heart of stimuli originating in the wall of the pulmonary artery and mediated by medullary centers which might account for sudden death. The pulmonary artery was distended, both with and without occlusion, but no effect was demonstrated on aortic blood pressure, cardiac rate or output per beat.

The electrocardiographic changes found in typical cases of pulmonary embolism have been defined by McGinn and White<sup>15</sup> and by Barnes<sup>16</sup>. McGinn and White

10 Jesser, J. H., and de Takáts, G. Visualization of Pulmonary Artery During Its Embolic Obstruction, *Arch Surg* **42** 1034-1041 (June) 1941.

11 Katz, L. N. Personal communication to the authors.

12 Scherf, D., and Schonbrunner, E. (a) Ueber Herzbefunde bei Lungenembolien, *Ztschr f klin Med* **128** 455-471, 1935, (b) Ueber den pulmocoronaren Reflex bei Lungenembolien, *Klin Wchnschr* **16** 340-344 (March 6) 1937.

13 Mann, F. C. Pulmonary Embolism. An Experimental Study, *J Exper Med* **26** 387-394 (Sept) 1917.

14 Hall, G. E., and Ettinger, G. H. An Experimental Study of Pulmonary Embolism, *Canad M A J* **28** 357-368 (April) 1933.

15 McGinn, S., and White, P. D. Acute Cor Pulmonale Resulting from Pulmonary Embolism. Its Clinical Recognition, *J A M A* **104** 1473-1480 (April 27) 1935.

16 Barnes, A. R. Diagnostic Electrocardiographic Changes Observed Following Acute Pulmonary Embolism, *Proc Staff Meet, Mayo Clin* **11** 11-13 (Jan 2) 1936.

lumen was occluded, the animals invariably died. In this regard it is of interest to note that Mann and his associates<sup>6</sup> demonstrated that constriction of the lumen of small arteries in animals may be surprisingly great without changing the rate of flow through the artery as measured by the thermistor-muhr. The cross-sectional area of the lumen may be reduced 50 per cent without any change of blood flow, while a reduction of 90 per cent of the area of the lumen reduces the flow only 50 per cent.

Villaret, Justin-Besançon and Bardin<sup>7</sup> reported their experimental work with rabbits in 1936. They were impressed with the nervous factors involved in pulmonary embolism. They noted that by sectioning the vagus nerves of rabbits they could increase sevenfold the quantity of small particulate matter (particles of pumice stone 150 microns in diameter) necessary to produce sudden death. On the contrary, by sectioning the cervicodorsal sympathetic nerves they could produce sudden death with only a fourth as much particulate matter. The stimulus for the sudden death, which was considered to be a result of reflex action on the general circulation, was thought to arise in the terminal pulmonary arterioles. In similar experiments in which they used enamel pearls measuring from 2 to 8 mm in diameter, they were unable to produce death, either sudden or delayed, with from 50 to 100 pearls. There was likewise no great increase of respiration in these animals such as occurred when particulate matter was used. The size of the embolizing particles thus greatly altered the results of the experiment.

In animals in which the vagus nerves had not been sectioned, Villaret and his associates were able to demonstrate a protective action by atropine sulfate and ephedrine hydrochloride used in combination, in that these drugs delayed sudden death. Chemical factors also were found to have definite effects on the length of survival of rabbits. Sodium bicarbonate increased the survival one hour to several days, while hydrochloric acid increased the susceptibility to sudden death. The authors suggested that death from pulmonary embolism is due in part to reflex sympathetic inhibition in which shock is the resultant manifestation of the inhibition.

The effect on the circulation and the heart of embolism of the main pulmonary artery or of one of its larger branches has been a much pondered question in recent years. Leriche, Fontaine and Friedmann<sup>8</sup> quoted statistics indicating that 30 per cent of patients dying of pulmonary embolism have small or partial occlusion of the pulmonary artery or of its branches, while de Takáts, Beck and Fenn found that 20 per cent of their patients whose death was considered typical of pulmonary embolism presented "minor" pulmonary obstruction. Death in such cases is attributed to reflex vasoconstriction of the pulmonary arterial bed through the sympathetic nerves, which greatly increases the strain on the right ventricle and decreases the flow of blood to the left ventricle. Leriche and his co-workers advocated infiltration of the stellate ganglion with procaine hydrochloride in cases of pulmonary embolism in an effort to release this vasoconstriction. One of us (Barnes<sup>9</sup>) suggested intravenous use of papaverine hydrochloride in order to release the spasm of the smooth muscle in the small pulmonary arteries. Jesser

6 Mann, F. C., Herrick, J. F., Essex, H. E., and Baldes, E. J. The Effect on the Blood Flow of Decreasing the Lumen of a Blood Vessel, *Surgery* 4: 249-252 (Aug.) 1938.

7 Villaret, M., Justin-Besançon, L., and Bardin, P. Recherches sur la prevention experimentale des accidents consecutifs sur embolies pulmonaires, *Bull. et mem. Soc. med. d. hop. de Paris* 52: 941-944 (June 15) 1936.

8 Leriche, R., Fontaine, R., and Friedmann, L. L'infiltration stellaire est-elle justifiee dans l'embolie pulmonaire du point de vue physiologique et anatomo-pathologique? Quelle place doit-elle occuper dans la therapeutique de cette affection? *J. de chir.* 50: 737-748 (Dec.) 1937.

9 Barnes, A. R. Pulmonary Embolism, *J. A. M. A.* 109: 1347-1353 (Oct. 23) 1937.

of the left ventricle is attributed by those authors to diminished flow through the right coronary artery resulting from increased tension in the right ventricle

The purpose in the present investigation is to study the heart in cases of pulmonary embolism. Particular attention is given to the location of any anatomic changes and to the frequency of these changes. A correlation of interesting electrocardiographic alterations with anatomic abnormalities is made.

#### METHOD OF STUDY

Protocols from a six year period (1935-1941) were consulted and 307 cases of pulmonary embolism were studied. The cases were divided roughly into surgical (70 per cent), medical (20 per cent) and cardiac (10 per cent). The number of surgical cases is unusually high compared with the data of Hampton and Castleman,<sup>20</sup> who gave the statistics from a large general hospital as surgical 40 per cent, medical 30 per cent and cardiac 30 per cent. Thirty cases were selected for careful anatomic study of the heart, as defined in the succeeding paragraphs. An endeavor was made to select (1) cases in which there had been clinical evidence of more than one pulmonary embolism (12), (2) cases in which there had been clinical evidence of shock for more than two hours before death (10) and (3) cases in which there was moderate to severe coronary sclerosis at necropsy (8). The embolism was considered as the primary cause of death in 26 cases and as only contributory to death in 4.

In each case the heart was examined grossly for evidence of dilatation of both auricles and ventricles and measurements were made of the thickness of the walls of each ventricle. The heart muscle was examined for evidence of fresh infarction, healing infarction and healed infarction. The interventricular septum and the posterior portion of the left ventricle were sectioned as well as the anterior portion of the left ventricle. At least six sections were made for microscopic examination as follows: (1) the anterior portion of the left ventricle, (2) the anterior portion of the right ventricle, (3) the posterior portion of the right ventricle, (4) the posterior basilar portion of the left ventricle, (5) the interventricular septum and (6) the posterior papillary muscle. A few sections were made of the anterior papillary muscle, and sections were taken from any scarred region or one suspicious of fresh infarction. The coronary arteries were then examined, and each artery together with its major branches was cut crosswise at least every 5 mm. Sections were taken from the artery in any region where there was significant encroachment on the lumen of the artery or where there was evidence of a thrombus. The distribution of each artery was noted, and, especially in regard to the posterior region of the left ventricle, note was made as to whether the right coronary or the left circumflex coronary artery supplied this portion.

The sections of heart muscle were examined microscopically for evidence of acute infarction or healing infarction which might have occurred concomitantly with a clinical episode of pulmonary embolism. In the study of any healing process of the myocardium, advantage was taken of the Van Gieson stain for fibrous tissue in estimating the age of the infarct.

#### RESULTS

In the study of 307 cases in which emboli were found in the pulmonary arteries at necropsy, the heart was found to weigh more than 400 Gm. in about a third of the cases. This did not include those in which there had been valvular or pericardial disease and was considered as evidence to indicate that there had been hypertension. When the medical cases were discarded and only the surgical ones were considered, the percentage in which the heart weighed more than 400 Gm. remained about the same (fig. 1).

Since practically all the patients who had had pulmonary embolism had been 50 or more years of age, a control group was studied of patients more than 50 years of age who had undergone a surgical operation and who had died of some cause other than pulmonary embolism (fig. 2). No significant difference in percentage of cases in which the heart weighed more than 400 Gm. was noted in the surgical group with pulmonary embolism and a control group with the same age distribution,

<sup>20</sup> Hampton, A. O., and Castleman, B. Correlation of Postmortem Chest Teleroentgenograms with Autopsy Findings, with Special Reference to Pulmonary Embolism and Infarction, *Am J Roentgenol* **43** 305-326 (March) 1940.

suggested that probably the changes in the electrocardiogram were due to "dilatation and partial failure of the chambers of the right side of the heart" These authors observed the following electrocardiographic changes in cases of pulmonary embolism (1) prominent  $S_1$  with S-T segment starting slightly below the base line, (2) depressed RS-T segment in lead II with gradual ascent from the S to the T wave in lead II, (3) usually a diphasic or monophasic  $T_2$ , (4) Q wave and definite inversion of T wave in lead III, (5) positive T wave, occasionally diphasic, in Wolferth lead It must be remembered that a typical case of pulmonary embolism may present all of these features, while cases in which there are smaller emboli may present any one or more characteristics of the electrocardiographic pattern

Although strain on the right ventricle with or without resultant failure plays some role, it has been pointed out by various authors that other factors possibly come into play in the complicated physiologic consequences of pulmonary embolism Edens was credited by Horn, Dack and Friedberg<sup>17</sup> with first suggesting that vagal stimulation rather than obstruction of the pulmonary artery is responsible for cardiac dysfunction and death, although no mention is made of this effect on the electrocardiogram Scheif and Schonbrunner<sup>12a</sup> attributed the electrocardiographic changes from 2 of 10 dogs in which experimental pulmonary embolism had been produced to reflex constriction of the coronary arteries with resultant decreased coronary flow Love and Brugler<sup>18</sup> suggested other than mechanical factors, such as anoxemia of the heart muscle, reflex changes in coronary circulation and the preexisting state of the coronary arteries

Love, Brugler and Winslow,<sup>19</sup> using dogs, studied the electrocardiographic changes occurring after experimental pulmonary embolism and emphasized the element of shock and the status of the coronary arteries in the electrocardiographic picture Shock produced by hemorrhage was found not to alter the electrocardiogram By partially ligating the anterior descending coronary artery and then inducing shock by hemorrhage, they produced elevation of the RS-T segment in leads II and III, simulating coronary occlusion Experimental embolization in 13 dogs revealed that depression of the S-T segment in lead II was the finding of most significance, which at times was accompanied by inversion of the T waves in leads II and III Comparable results were obtained by mechanical obstruction applied externally to the pulmonary artery No alteration of these electrocardiographic findings was noted after vagal or sympathetic denervation

Anatomic changes in the hearts of patients who died of pulmonary embolism have been described recently Horn, Dack and Friedberg studied the records of 42 cases of pulmonary embolism and found structural myocardial changes "ordinarily resulting from acute myocardial ischemia" in 8 (minimal in 4) The location of these changes they did not define except to state that the sections were taken from the left ventricle The electrocardiographic pattern in cases of pulmonary embolism is attributed by these authors to myocardial ischemia from coronary insufficiency as a result of the interplay of three probable factors (1) shock, (2) asphyxia and (3) exaggerated vagal reflexes from obstruction of the pulmonary arteries The similarity of the electrocardiographic changes in cases of pulmonary embolism and cases of myocardial infarction of the posterior wall

17 Horn, H, Dack, S, and Friedberg, C K Cardiac Sequelae of Embolism of the Pulmonary Artery, *Arch Int Med* **64** 296-321 (Aug) 1939

18 Love, W S, Jr, and Brugler, G W Electrocardiograms Similar to Those of Coronary Thrombosis with Especial Reference to Those Obtained in Pulmonary Embolism, *South M J* **30** 371-375 (April) 1937

19 Love, W S, Jr, Brugler, G W, and Winslow, N Electrocardiographic Studies in Clinical and Experimental Pulmonary Embolization, *Ann Int Med* **112** 2109-2123 (June) 1938

and the average weight of the heart in the two groups was almost the same. Thus it may be concluded that among patients who had enlarged hearts and who underwent a surgical operation pulmonary embolism was no more likely to develop than among patients who had hearts of normal weight. If it is admitted that in this study hypertrophied hearts were considered to indicate hypertensive vascular disease, it is apparent that hypertension did not predispose to pulmonary embolism (figs 1 and 2).

The medical cases in which pulmonary embolism occurred consisted mainly of two groups: those in which there was heart disease with signs of congestive heart failure most commonly due to hypertensive heart disease alone or combined with coronary sclerosis, and those in which there was some wasting disease (cancer or senility). The curve of the weight of the heart for the medical group (fig 3) is

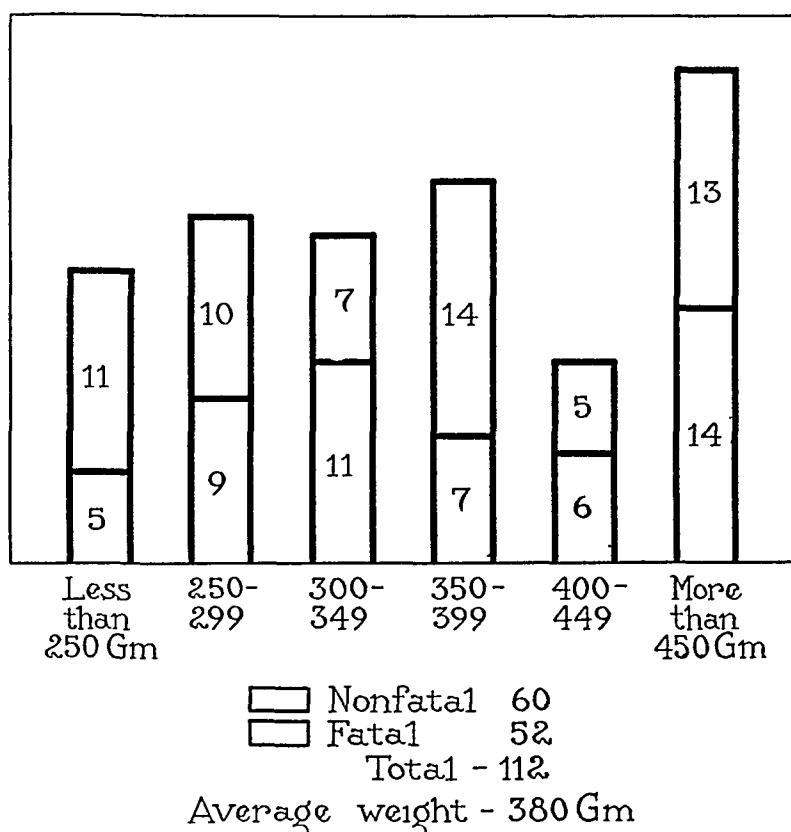


Fig 3—Weights of the hearts of medical patients who had pulmonary embolism

considerably "flatter" than that for the surgical group, since in the group of cases in which there was a wasting disease the number in which the heart weighed less than 250 Gm tended to increase and in the group of cases in which there was hypertension the opposite was observed. It also will be noted that the percentage of cases in which the pulmonary embolism was fatal was considerably less in the medical group (46 per cent) than it was in the surgical group (74 per cent). This confirms the general clinical impression that the percentage of cases with fatal pulmonary embolism is greater in the surgical than in the medical group.

Among the 30 cases of pulmonary embolism studied, there were 5 in which the anatomic changes in the heart muscles were significant. They are presented here.

*Myocardial Infarction Without Coronary Occlusion*—In 4 cases recent myocardial infarction was observed, but no thrombosis or occlusion of the coronary arteries could be demonstrated. The location and extent of the infarction varied.



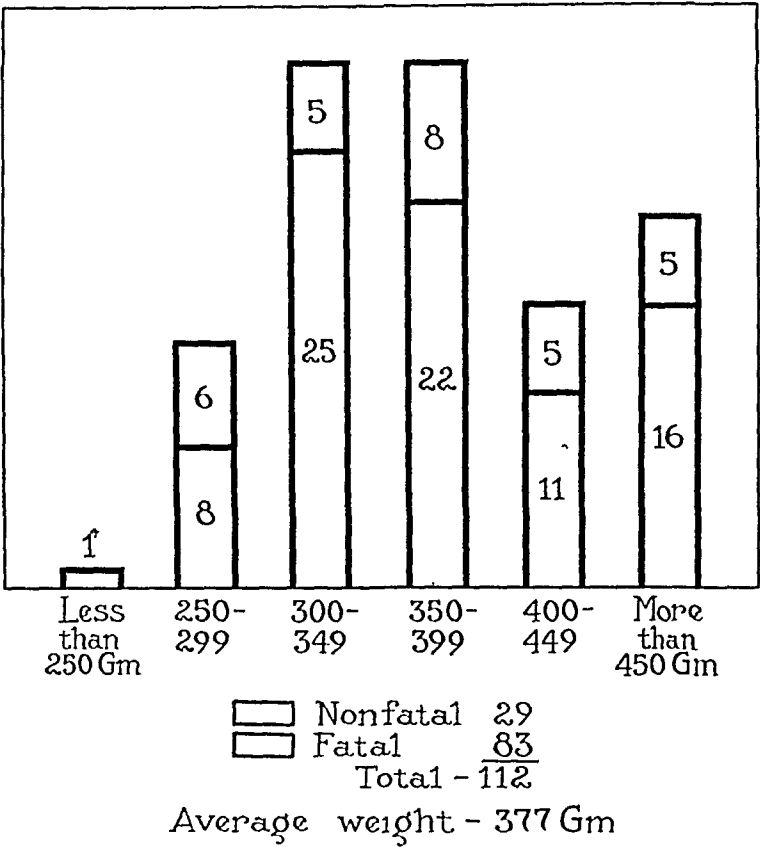


Fig 1—Weights of the hearts of surgical patients who had pulmonary embolism

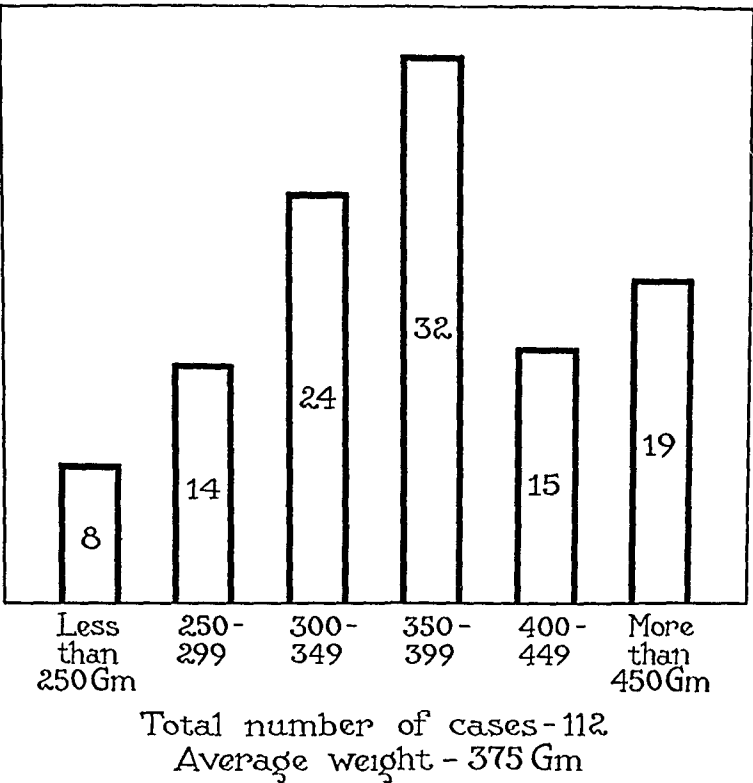


Fig 2—Weights of the hearts of surgical patients more than 50 years of age and without pulmonary embolism

designates the least amount of sclerosis and 4 the greatest) The left circumflex artery was patent, and the sclerosis was graded 2 Five centimeters from the orifice of the left descending coronary artery was an old thrombus, which had become recanalized but which occluded about 95 per cent of the lumen of the artery Sclerosis of this artery was graded 3 The region of recent infarction in the posterior portion of the right ventricle was located in the apical third and was recognized grossly (fig 5 *a*) Microscopic examination of this region revealed loose connective tissue, which did not take the Van Gieson stain, and occasional collections of lymphocytes There were a few small scattered regions in the posterior portion of the left ventricle which appeared fibrotic and which on microscopic examination proved to be regions of recent infarction They were present in both the apical and the basilar portions (fig 5 *b*) No polymorphonuclear leukocytes were found The age of these infarctions was estimated at about three weeks<sup>21</sup>

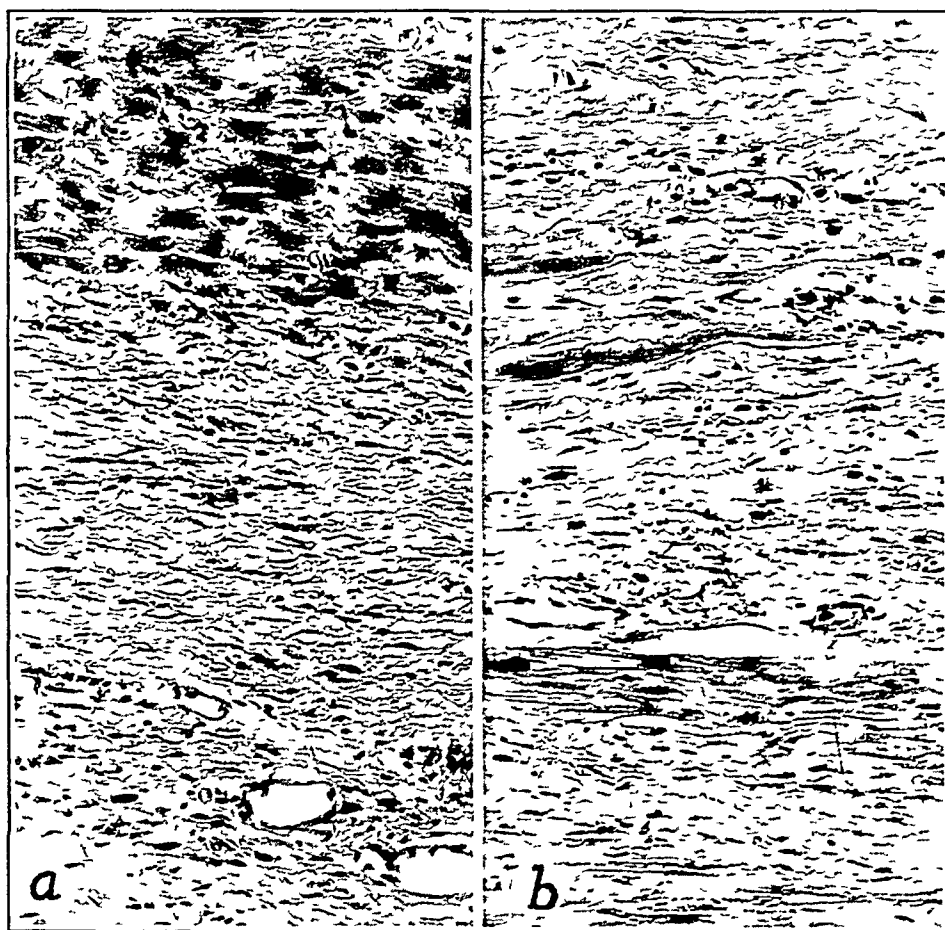


Fig 5—(*a*) Section from the posterior portion of the right ventricle close to the epicardial surface, representing healing infarction The loose fibrous tissue does not take the Van Gieson stain (*b*) Section from the posterior portion of the left ventricle close to the interventricular septum demonstrated focal healing infarction The fibrous tissue does not stain with the Van Gieson stain and is of approximately the same age as that in *a*

Case 1 illustrates the difficulties which may present themselves at times to one making a diagnosis of pulmonary embolism The clinical picture of tachycardia, dyspnea and cyanosis, followed on the fifth day by the spitting of blood, was sufficient to allow a diagnosis of pulmonary embolism with pulmonary infarction to be made Yet the electrocardiogram taken on the second day presented the typical  $Q_s T_s$  pattern of myocardial infarction of the posterior wall It will be

21 Mallory, G K, White, P D, and Salcedo-Salgar, J The Speed of Healing of Myocardial Infarction A Study of the Pathologic Anatomy in Seventy-Two Cases, *Am Heart J* 18:647-671 (Dec) 1939

CASE 1—A 64 year old man was admitted to the hospital for litholapaxy and transurethral prostatic resection. His history did not suggest previous heart disease, and his blood pressure was 130 mm of mercury systolic and 80 diastolic. Operation was performed, with the patient under spinal anesthesia, on Nov 18, 1940. November 20, on returning to bed after sitting in a chair, he became weak, his pulse rate rose to 130, his respiratory rate increased to 36, and he appeared cyanotic. The temperature rose to 103 F. His condition was improved considerably after he had spent eight hours in an oxygen tent, at which time the blood pressure was 125 mm of mercury systolic and 80 diastolic. An electrocardiogram taken on November 21 revealed a typical  $Q_s T_s$  pattern with a slight lengthening of the S wave in lead I (fig 4). On November 24 the patient raised small amounts of bright red sputum. Convalescence was uneventful thereafter until December 5, when he complained of a pleuritic pain in the lower right portion of the chest. On the following day he experienced tenderness in the right calf, and the temperature rose to 101 F, although the right leg did not become swollen. The temperature returned to normal on the following day, and

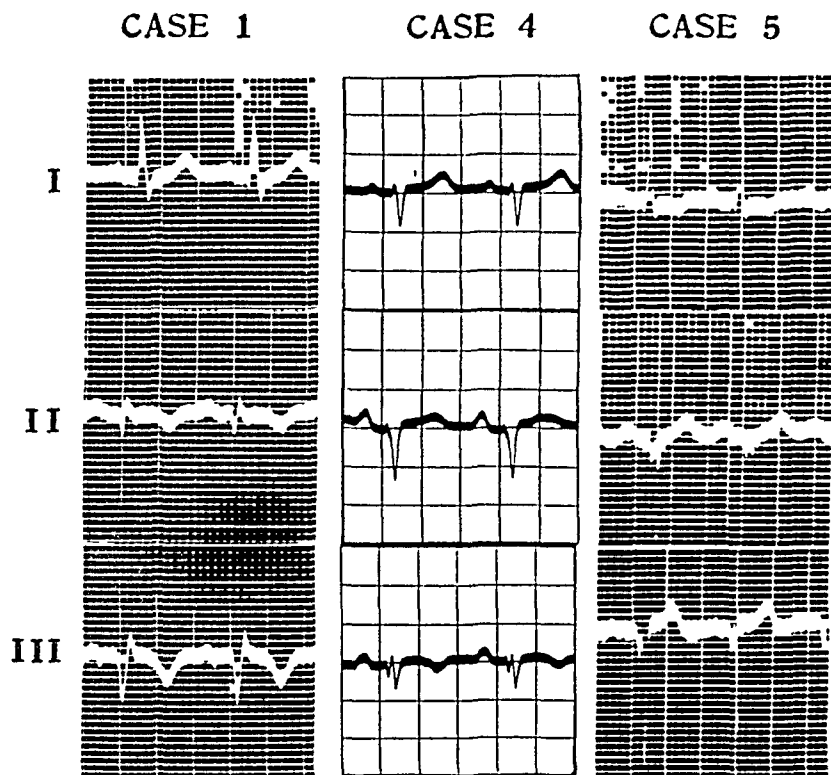


Fig 4—Case 1 The electrocardiogram was taken one day after an episode of pulmonary embolism and presents a typical Q wave-T wave pattern in lead III plus slight prolongation of the S wave in lead I

Case 4—The electrocardiogram, taken on the day of death, presents a much elongated S wave in lead I and a small Q wave and an inverted T wave in lead III. The greater deflection in each lead is negative.

Case 5—This tracing, taken before the onset of pulmonary edema and ten hours before death, reveals only evidence of left ventricular strain and nothing to suggest pulmonary embolism or myocardial infarction.

the patient was improving until he suddenly collapsed, became cyanotic and dyspneic, and died within thirty-five minutes, on December 8.

The anatomic diagnosis was (1) fatal pulmonary embolism (source, right iliac vein) (residual thrombus in left iliac vein), (2) multiple pulmonary infarcts with focal pleuritis, (3) hypertrophy of the heart (580 Gm), (4) healed myocardial infarction of the anterior portion of the interventricular septum (6 by 3 cm) and healing recent myocardial infarction of the posterior portion of the left ventricle adjacent to the interventricular septum (focal) and the posterior portion of the right ventricle (2 by 2.5 cm).

The right coronary artery supplied the posterior basilar portion of the left ventricle and was patent throughout. The sclerosis was graded 1 (on the basis of 1 to 4, in which 1

carcinoma of both ovaries with peritoneal implants was revealed, and bilateral salpingo-oophorectomy was performed. On April 10, the temperature rose to 102 F, the pulse rate to 160 and the respiratory rate to 50. The patient was markedly dyspneic, and there was cyanosis of the skin. The patient was considered to have pneumonia in the lower lobe of the right lung and received sulfapyridine (2-[paraaminobenzenesulfonamido]-pyridine). She continued to improve until April 22, when she suddenly became cyanotic and pulseless and died within five minutes.

The anatomic diagnosis was (1) bilateral fatal pulmonary embolism with pulmonary infarcts of the right lung (source, right femoral vein), (2) adenocarcinoma of both ovaries with peritoneal carcinomatosis (ascites, 5 liters), (3) recent myocardial infarction of the apex of the interventricular septum (0.3 cm in diameter) and microscopic foci in the anterior wall of the right ventricle and the posterior papillary muscle, (4) bilateral hydrothorax (right, 350 cc, and left, 300 cc) and (5) evidence of old right radical mastectomy for adenocarcinoma grade 4.

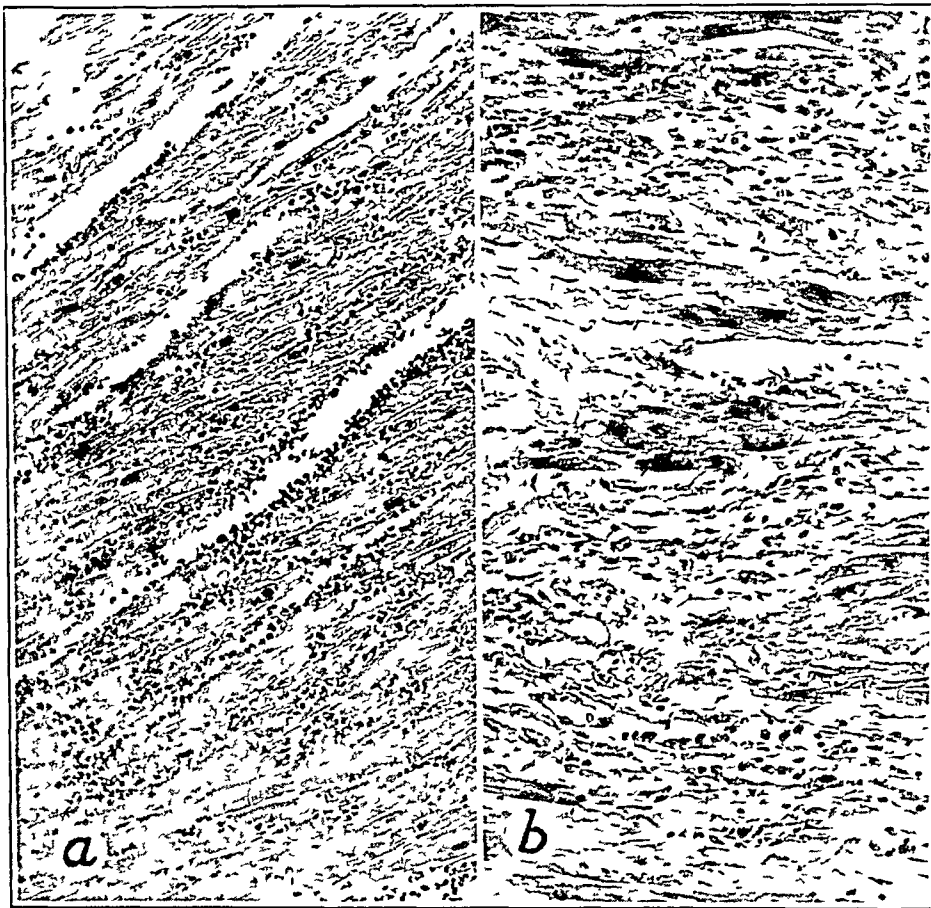


Fig 6—(a) Region of acute infarction from the posterior basilar portion of the left ventricle corresponding to that described grossly. (b) Section from the small region located in the interventricular septum at the apex noted grossly. The section demonstrates a recent small healing infarction.

The heart weighed 340 Gm, and the sclerosis in all the coronary arteries was graded 1. The regions of healing infarction were consistent with a healing of about two weeks (fig 6b).

In case 3 the diagnosis of pulmonary embolism was not made clinically, and the patient was treated for suspected pneumonia of the lower lobe of the right lung after the rather sudden onset of dyspnea and cyanosis twelve days before death. The second embolism resulted in death within a few minutes. From analysis of the case at necropsy, it seems most likely that the recent infarction of the myocardium occurred at the time of the first embolism, at which time the pulse rate rose to 160 and the respiratory rate to 50. No electrocardiogram was taken in this case.

noted, however, that the S wave in lead I measures 2 mm, which might be construed as evidence of pulmonary embolism. Since no thrombosis or occlusion was found in the right coronary artery supplying the posterior portion of the heart, it seems justifiable to assume that the regions of recent infarction which were found resulted from a decrease in blood flow to these portions of the heart at the time of the pulmonary embolism.

CASE 2—A 53 year old woman entered the hospital, complaining of epigastric pain and gas immediately after eating, of six weeks' duration. During the preceding year she had lost 40 pounds (18 Kg). Her history did not suggest heart disease, and her blood pressure was 140 mm of mercury systolic and 90 diastolic. The heart was normal to examination. There was a large irregular nodular mass which seemed to fill the epigastrium and was not attached to the liver. On May 7, 1940, redness and pain developed over the dorsum of the right foot, and in this region a firm, tender vein was palpated. Abdominal exploration was performed on May 10, and on the following day the patient complained of pain in the whole left leg, which soon was swollen and cyanotic. Tenderness along the femoral vein was noted on May 12. On May 13 the patient became nauseated and vomited, but the pulse rate continued about the same, ranging between 100 and 120. The patient became cold, sweaty and semistuporous and died on May 15. The blood pressure was recorded as 70 mm of mercury systolic and 50 diastolic six hours before death.

The anatomic diagnosis was (1) carcinoma of the stomach (limitis plastica type) with abdominal and peritoneal carcinomatosis and metastasis to the periaortic lymph nodes and the right adrenal gland, (2) pulmonary embolism of the right lung with pulmonary infarcts (source, thrombosis of both iliac veins with extension into the inferior vena cava), (3) hypertrophy of the heart (390 Gm) and (4) acute myocardial infarction (15 by 2 cm) of the posterior base of the left ventricle, located 3 cm from the interventricular septum.

The right coronary artery supplied the greater portion of the posterior wall of the left ventricular, including the region of acute infarction. No thrombi or occlusions were found in the coronary arteries, and the coronary sclerosis was graded as follows: left descending artery, grade 2, left circumflex artery, grade 3, right artery, grade 3. The region of acute infarction presented infiltration with polymorphonuclear cells, loss of striation of some of the muscle bundles, eosinophilic staining of some muscle and scattered regions of hemorrhage (fig 6a). There were multiple small emboli in the arteries of the right lung, with one infarct, measuring 3 by 2 cm, in the upper lobe of this lung. In the main artery to the lobe of the lung there was a riding embolus occluding the artery, which showed early organization with the pulmonary artery. At least half of this lower lobe showed evidence of hemorrhagic infarction. The estimated age of both the myocardial infarction and the embolism in this lobe with pulmonary infarction was from two to four days.

In case 2 the pulmonary emboli were considered to be only contributory to death since only a part of the pulmonary arterial tree was obstructed and since death was at least partially due to the generalized carcinomatosis. Here again there was no demonstrable occlusion of the right coronary artery, which supplied the portion of the heart which was infarcted, although the sclerosis of this artery was graded 3. The most reasonable explanation for the infarction of the heart was that the flow of blood through the right coronary artery was insufficient. This was thought to be due essentially to two factors: (1) the shock which was manifest clinically for at least two days before death, and (2) the coronary sclerosis which was particularly evident in the long right coronary artery which supplied the infarcted region. Pulmonary embolism and general debility were the causative factors for the state of shock.

CASE 3—A 57 year old woman complaining of a lump in the right breast was examined at the clinic in March 1938. Radical mastectomy was performed at this time, revealing adenocarcinoma of grade 4 (Broders' method) without involvement of the lymph nodes. She remained well until February 1939, when she noticed gradual enlargement of the abdomen and returned to the clinic in April of the same year. Her blood pressure was 140 mm of mercury systolic and 88 diastolic, and her history was not suggestive of heart disease. At this time an irregular mass, about 5 cm in diameter, was noted to the left of the uterus. Abdominal exploration was carried out on April 8, 1939, and extensive adeno-

occurred during or after the episode noted on November 13, at which time the patient had another pulmonary embolism. The acute infarction was particularly remarkable in the interventricular septum in the region of the pulmonary conus (fig 7 *b*) and the papillary muscles of the right ventricle, suggesting that decreased coronary arterial blood flow, as a result of greatly increased pressure in the right ventricle, was the cause of the infarction. The electrocardiogram was suggestive of a greatly increased strain on the right ventricle. Death in this case was apparently the result of failure of the right ventricle, since no embolism was found which was not partially organized to the pulmonary artery.

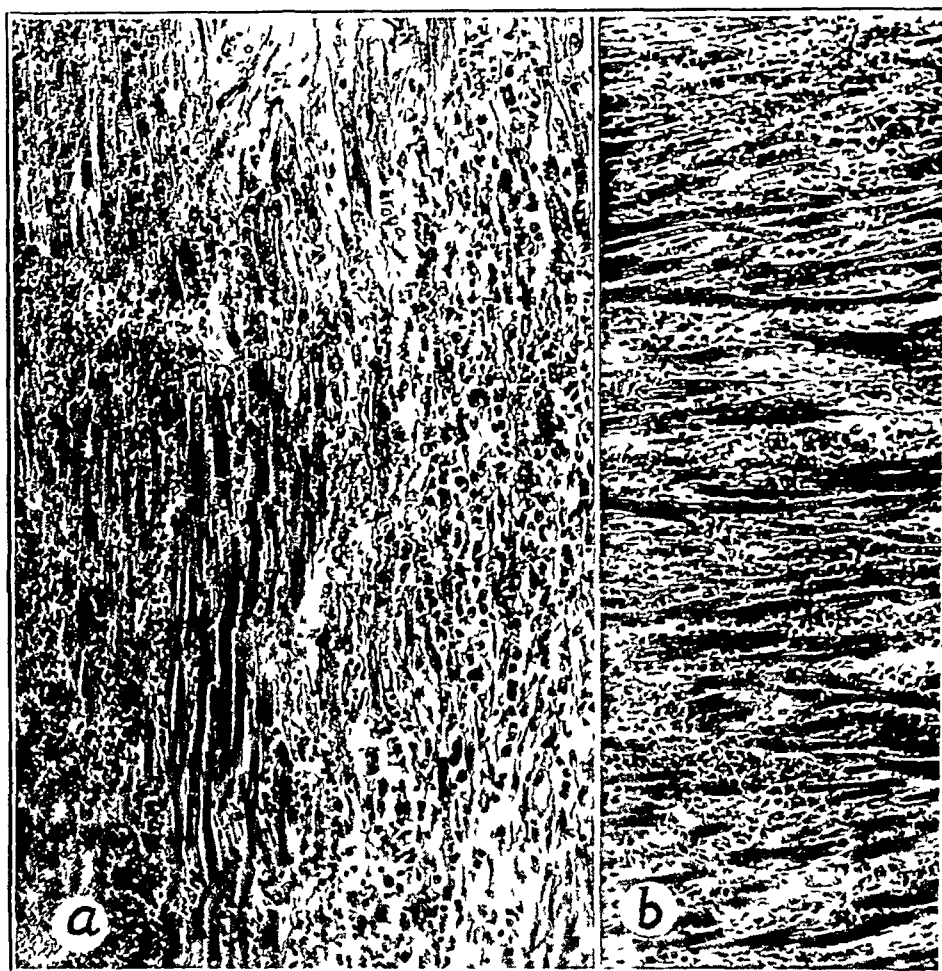


Fig 7—(a) Section from the region of acute infarction at the apex of the left ventricle. It reveals healing infarction on the right and acute infarction with hemorrhage on the left. (b) Section from the interventricular portion of the conus arteriosus, demonstrating acute infarction with many polymorphonuclear cells without hemorrhage. This infarction is quite extensive.

The history of the abdominal ascites, followed by pleural effusion, both responding to small doses of roentgen therapy, suggests that both were due to metastasis from the uterine carcinoma, which was quite radiosensitive. Inoculations of the fluid into guinea pigs gave negative results, and the only evidence of tuberculosis at necropsy was the presence of calcified hilar lymph nodes.

*Myocardial Infarction with Coronary Occlusion*.—One case was encountered in which the myocardial infarction was associated with recent thrombosis of the coronary artery.

**CASE 5**—A 53 year old man entered the hospital on Oct 27, 1940, complaining of marked dyspnea and intermittent nocturnal dyspnea of one month's duration. Three years before entering,

CASE 4—A 46 year old woman entered the clinic in October 1939, complaining of gradual abdominal distention and loss of weight. She had lost 15 pounds (6.8 Kg) in the five weeks before entry.

The blood pressure was 120 mm of mercury systolic and 80 diastolic. The heart was normal, and there was abdominal distention of grade 2 with shifting dullness. Abdominal exploration at this time revealed the presence of 4.5 liters of reddish straw-colored fluid and generalized peritonitis with considerable injection of the peritoneum. Inoculation of the fluid into guinea pigs gave negative results for tuberculosis, and biopsy of the omentum gave negative results for a malignant growth. On the seventh postoperative day the patient had right iliofemoral thrombophlebitis, which subsided without subsequent swelling. She received twelve roentgen treatments to the abdomen shortly after operation.

She returned in January 1941, complaining of shortness of breath, at which time she was found to have a pleural effusion on the left side. Diagnostic thoracentesis was performed, and the fluid on inoculation in guinea pigs proved to be negative for tuberculosis. The patient was given two roentgen treatments to the left side of the chest, and the effusion subsided.

In June 1941 she began to have intermittent bloody discharge from the vagina but otherwise remained in good health. On November 7 she was awakened at night by a severe pain in the left side of the chest which extended down the left arm. The pain lasted one hour, during which time she was dyspneic and after which she complained of weakness. Another similar episode occurred on November 13, and the patient entered the hospital on November 15 because of considerable shortness of breath on exertion.

The blood pressure was 140 mm of mercury systolic and 86 diastolic. The chest revealed no abnormality. To the left of the sternum toward the apex of the heart a diastolic gallop rhythm was heard. The patient was moderately dyspneic, with moderate cyanosis and pallor of the lips. The electrocardiogram taken on November 18 showed that the chief initial ventricular deflection was normal in all three limb leads, with an elongated S wave in lead I, an inverted T wave in lead III and a notched QRS complex in lead III (fig 4). No chest leads were taken.

The patient remained quite dyspneic and somewhat restless, with considerable relief of the dyspnea on breathing 100 per cent oxygen. The venous pressure measured 22 cm of water on November 18. Later the same day a severe pain developed in the left lower anterior portion of the chest, followed by vomiting and profound shock. The blood pressure and the pulse were imperceptible, and the patient died thirty-five minutes later.

The anatomic diagnosis was (1) thrombosis of the right iliac vein with bilateral organizing emboli, (2) thrombosis of a small distal branch of the anterior descending coronary artery with acute and healing myocardial infarcts (1 to 2 cm in diameter) at the apex of the left ventricle, (3) acute and healing myocardial infarcts of the interventricular septum in the region of the pulmonary conus, of multiple papillary muscles of the right ventricle, of the anterior papillary muscle of the left ventricle and of the posterior wall of the left ventricle and the interventricular septum, (4) dilatation of the right ventricle, grade 3, with mural thrombi, (5) polypoid carcinoma of the uterus with metastasis to the aortic lymph nodes and (6) chronic passive congestion of the liver with central necrosis.

The thrombus found in the branch of the left descending coronary artery only partially occluded the artery and was partially organized. The age of this thrombus and the surrounding early healing infarct of the myocardium (fig 7a) was estimated at about twelve to fourteen days. No freshly thrombosed arteries were found to account for the adjacent acute infarction at the apex of the left ventricle or the acute and healing regions of infarction found in the other locations of the heart. Coronary sclerosis was equal throughout all the arteries and was grade 1. The right auricle was dilated (grade 2) and the right ventricle measured 0.5 cm in spite of the considerable dilatation.

Even though thrombosis was found in one small branch of a coronary artery, case 4 is classified in this group since no thrombosis was found to account for the other regions of both acute and healing myocardial infarction which were observed. It will be noted also that the thrombus found in the branch of the left descending coronary artery only partially occluded the lumen. This region of healing infarction at the apex as well as the other smaller regions of healing infarction were thought to have occurred on November 7, at which time the patient apparently had a good-sized pulmonary embolus. The pain in the chest with extension down the left arm was probably due to the infarction of the heart that took place at that time. The more acute infarcts were estimated to be less than seven days old and probably

had a slight cough during this time and raised small amounts of yellow-colored sputum. During the three months he had lost 40 pounds (18 Kg.)

The patient was well developed but appeared chronically ill and was sweating moderately. His blood pressure was 130 mm of mercury systolic and 80 diastolic, his pulse rate 68 and his respiratory rate 20. There was dullness to percussion and decreased breath sounds over the entire chest, especially the lower half. The cardiac rhythm was regular, and there was a grade 2 systolic murmur at the apical and the aortic areas of the heart. A roentgenogram of the chest revealed complete opacity of the entire left side of the chest with a shift of the heart and the mediastinum to the left. A roentgenogram of the chest taken with the use of a Bucky diaphragm revealed a tumor mass in the left upper part of the chest, extending to the level of the ninth rib posteriorly, and elevation of the left side of the diaphragm. The concentration of hemoglobin was 10.2 Gm per hundred cubic centimeters of blood. The serologic reaction for syphilis was 4 plus. Bronchoscopic examination on three occasions revealed a large tumor mass which almost completely obstructed the left main bronchus, located at the bifurcation of the left upper and the left lower bronchus. Biopsy revealed only inflammatory tissue.

On the evening of April 6 the patient fainted after straining at stool, the pulse rate rose to 120, and the blood pressure was 100 mm of mercury systolic and 70 diastolic. On the following morning he passed a tarry stool. At 9 p. m. on April 7 the patient suddenly became semicomatose and pale, with a pulse rate of 154, and the blood pressure was unobtainable. Shortly thereafter he passed a large bloody stool involuntarily. The patient remained irrational, his skin was pale and cyanotic, and his blood pressure remained imperceptible. His pulse rate ranged from 120 to 160. He was given three blood transfusions without improvement and died fifty-four hours after the onset of shock.

The anatomic diagnosis was (1) syphilitic aortitis with aneurysmal formation of the arch of the aorta and extension of the aneurysm into the esophagus and the left main bronchus, (2) rupture of the aneurysm into the esophagus with gastrointestinal hemorrhage (2,000 cc.), (3) atelectasis of the upper lobe of the left lung with bronchiectasis, (4) hypertrophy of the heart (510 Gm.), (5) acute infarction of the posterior wall of the left ventricle in the middle third, measuring 2 by 1.5 cm., and of the posterior papillary muscle (fig. 8a and b).

The coronary sclerosis was minimal and was graded accordingly: (1) left descending artery, grade 1, (2) left circumflex artery, grade 1, (3) right coronary artery, grade 2. The orifice of the right coronary artery measured 2 by 2.5 mm and was thought to be narrowed slightly by the syphilitic process of the aorta. The right coronary artery supplied the posterior wall of the left ventricle in the region in which the acute infarction was found.

Case 6 illustrates what may happen in the heart as a result of severe, prolonged shock. Two factors should be considered: (1) the decreased coronary arterial flow as a result of the great drop of blood pressure, both systolic and diastolic, and (2) the definite anoxia, evidenced by the persistent cyanosis in the presence of moderate anemia.

*Pulmonary Embolism with Electrocardiographic Changes but Without Myocardial Infarction*—These cases are presented to illustrate the large group of cases in which, despite pulmonary embolism, no anatomic changes could be demonstrated in the myocardium. In the first case infarction of the posterior wall of the left ventricle was diagnosed clinically, chiefly by the electrocardiographic limb leads. In the second case the clinical picture was suggestive of pulmonary embolism and the electrocardiographic chest leads confirmed the diagnosis.

**CASE 7**—A 66 year old laborer entered the hospital on Aug. 25, 1939 because of two recent episodes of pain in the chest and dyspnea. On August 11 he had walked to the bathroom at 4 a. m., and while sitting on the stool, suddenly lost consciousness and was unconscious eight to ten minutes. On regaining consciousness, he was severely dyspneic and was sweating profusely but was able to return to his bed. Two days later, after a large evening meal, he suddenly became faint, and a bandlike pain developed across the lower part of the chest. He was dyspneic and perspired a good deal. The pain subsided in a few minutes.

On August 22 he had experienced a second episode of pain in the chest with sweating and dyspnea.

He was a well developed, slightly obese man. His blood pressure was 132 mm of mercury systolic and 76 diastolic. His chest was clear, the heart sounds were distant but normal, and the pulse rate was 90.



he had had an episode of prolonged substernal pain lasting two days, which was considered to be due to coronary occlusion with myocardial infarction. Since that time his cardiac reserve had been decreased and he had noted angina on exertion. His blood pressure of 160 mm of mercury systolic and 110 diastolic. The heart was enlarged on examination, and the liver was palpable 2 fingerbreadths below the right costal border. On November 2 the patient had a sudden onset of severe pain in the right upper quadrant of the abdomen, extending to the back. At this time he was nauseated and vomited. The edge of the liver was tender to palpation, and the pulse rate rose to 120. Two days later he complained of pleuritic pain in the left side of the chest and raised bright red sputum.

Hemoptysis continued, and a friction rub developed over the left lower posterior portion of the chest. The patient's condition remained unchanged until November 8, then, after intravenous administration of 300 cc of a 20 per cent solution of dextrose, acute pulmonary edema developed, and he died six hours later. An electrocardiogram taken on November 8 revealed only left axis deviation, a depressed ST segment in lead I and an inverted T wave in lead I (fig. 4).

The anatomic diagnosis was (1) hypertrophy of the heart (620 Gm) with dilatation of the left ventricle, (2) bilateral pulmonary embolism with organization, (3) multiple bilateral pulmonary infarctions with formation of an abscess in the lower lobe of the right lung, (4) coronary sclerosis, grade 2, with recent thrombosis of the right coronary artery, (5) patchy regions of recent myocardial infarction of the right ventricle, of the posterior wall of the left ventricle and of the interventricular septum and (6) myocardial scarring in the anterior portion of the interventricular septum.

The heart was enlarged and both the left ventricle and the left auricle were dilated (grade 2). There was considerable sclerosis (grade 3) of the left circumflex and right coronary arteries, and several branches of the left descending artery were occluded by arteriosclerosis.

It is difficult in case 5 to follow the exact course of events, but it is apparent that the patient had long-standing coronary and hypertensive heart disease which was complicated in the end stage by multiple pulmonary emboli. The episode of pain and tenderness in the right upper quadrant of the abdomen was undoubtedly a manifestation of pulmonary embolism of the lower lobe of the right lung with involvement of the pleura. It is probable that at the same time thrombosis of the right coronary artery developed, since the estimated age of this thrombosis was approximately one week. The myocardial infarctions in the right ventricle, the posterior wall of the left ventricle and the interventricular septum were also recent and corresponded approximately to the age of the thrombosis of the right coronary artery.

It is interesting to note that there was no recent infarction in the region of the scar in the lower two thirds of the anterior wall of the left ventricle and the interventricular septum, where one might expect the blood supply to be poor as a result of the previous coronary occlusion. The electrocardiogram taken on the day of death does not reveal evidence of either the recent injury to the heart or the result of the previous coronary thrombosis with myocardial scarring. The recent myocardial infarction was not extensive enough to alter the electrocardiogram appreciably, while the old scar was located mainly in the anterior portion of the interventricular septum, which seldom affects the electrocardiogram unless one or more of the conducting bundles are destroyed. Chest leads might have been of diagnostic aid in this case but unfortunately were not obtained.

*Myocardial Infarction of the Posterior Wall of the Left Ventricle Resulting from Severe Prolonged Shock*—This case is presented as an illustration of what may occur in the heart as a result of severe prolonged shock without occlusion of a coronary artery.

**CASE 6**—A 54 year old man entered the hospital on March 9, 1941, complaining of recurrent chills and fever of three months' duration. The patient stated that for two weeks in January 1940 he had been quite hoarse, but that after this he was well until three months before entry, when recurrent episodes of chills and fever developed, with a rise of temperature to 104 F. He

sclerosis found at necropsy, the relief of pain in the chest afforded by the administration of glyceryl trinitrate suggests that the coronary blood flow had been diminished by spasm. If such an assumption should be correct, it would support the thought of some investigators that spasm of the coronary arteries may occur in conjunction with pulmonary embolism.

CASE 8—A 57 year old farmer was brought to the hospital on Nov 28, 1940, having been unconscious for two hours after an automobile accident. Soon after entry he underwent an

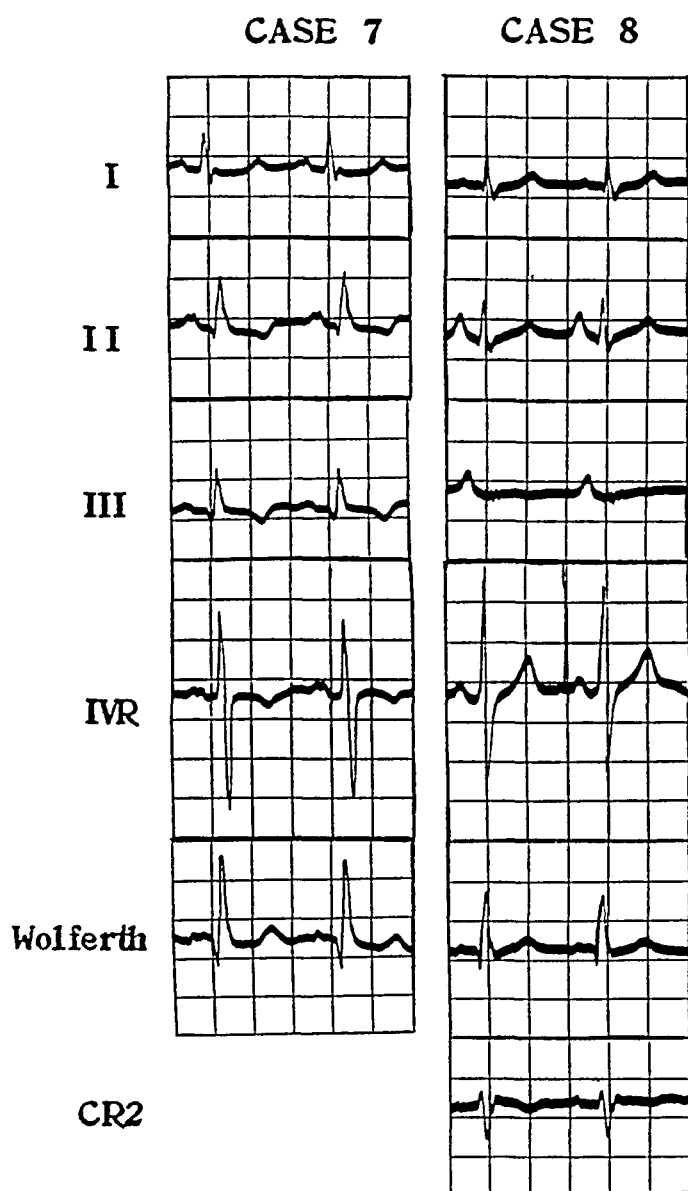


Fig 9—Case 7 The electrocardiogram, taken on Aug 31, 1939, shows an imperfect Q wave-T wave pattern in lead III with a slight prolongation of ST. The chest leads are particularly interesting since the T waves in the apical and Wolferth leads are the reverse of normal.

Case 8—The electrocardiogram, taken on Dec 24, 1940, reveals prominent P waves in leads II and III, a small ST and an isoelectric T. The chest leads are diagnostic of pulmonary embolism with a normal T wave in lead IV R and T waves in the CR<sub>2</sub>, and Wolferth leads the reverse of normal.

operation for decompression and elevation of a skull fracture. He responded well, and the course of his recovery was uneventful until December 14, when he complained of pleurisy in the right lower portion of the chest, and his temperature rose to 99.6 F. This subsided in two days, and he was dismissed from the hospital on December 21 to stay in a convalescent home.

On the night of August 30, the patient awoke with a steady epigastric pain associated with dyspnea and sweating, which was relieved by glyceryl trinitrate. On the following morning the same pain occurred after eating, and for the third time the same evening, at which time the pain was relieved again by glyceryl trinitrate. On September 1 the patient became extremely dyspneic and sweated profusely. Severe shock developed, with blood pressure and pulse imperceptible. He died twenty-five minutes after the onset of this final episode.

Four electrocardiograms were taken, which were similar. There was an imperfect Q wave-T wave pattern in lead III with inversion of the T wave in lead IV R and an abnormally positive T wave in the Wolkofsky lead (fig 9). The clinical diagnosis was considered to be myocardial infarction of the posterior wall of the left ventricle.

The anatomic diagnosis was (1) fatal pulmonary embolism, (2) hypertrophy of the heart (420 Gm).

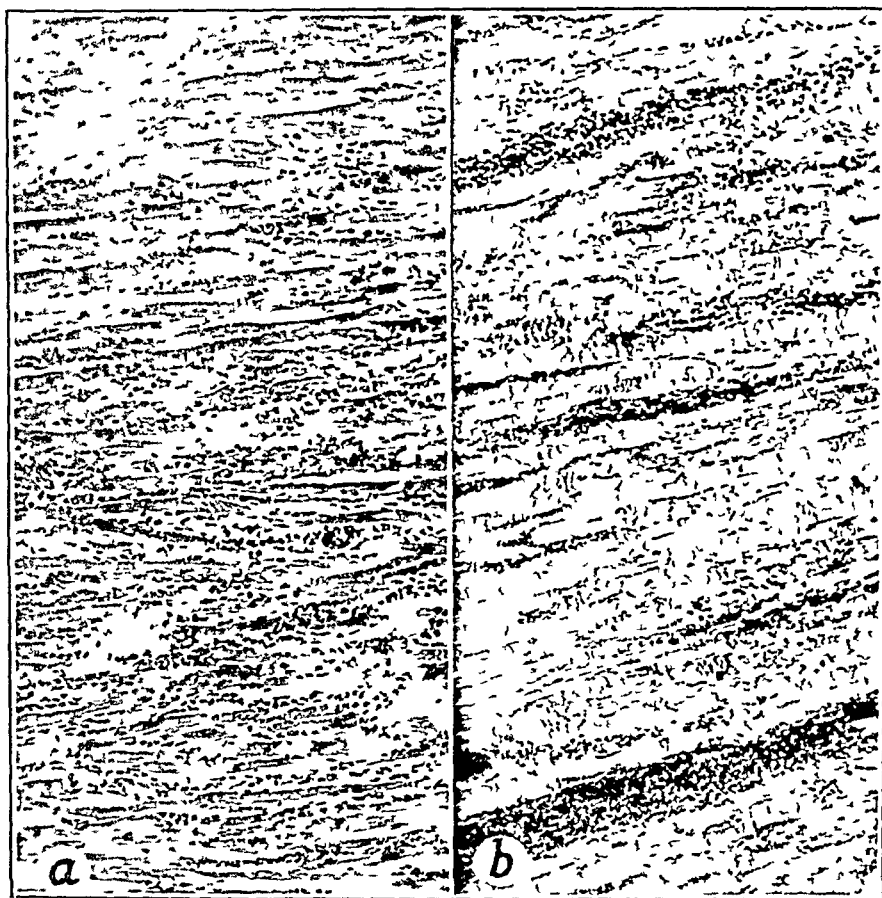


Fig 8—(a) Section from the posterior papillary muscle close to the tip demonstrating acute infarction, (b) region of acute infarction from the midportion of the posterior left ventricle adjacent to the interventricular septum. Regions of moderate hemorrhage and dilatation of the blood vessels are present.

Both the right auricle and the right ventricle were dilated (grade 3), and the thickness of the wall of the right ventricle averaged 0.7 cm. The thickness of the wall of the left ventricle measured 1.7 cm. The coronary sclerosis was graded 1, and no thrombi were found in the coronary arteries. Numerous sections of the myocardium, especially of the posterior wall of the left ventricle, were made and did not reveal any evidence of infarction.

Case 7 illustrates the pitfalls in distinguishing between pulmonary embolism and myocardial infarction of the posterior wall of the left ventricle in certain cases. Significant changes are demonstrable in the electrocardiographic limb leads and chest leads without morphologic change in the heart muscle. At the same time it is of interest to note that on three different occasions the patient was relieved of anginal pain by glyceryl trinitrate (Scherf). In view of the absence of significant coronary

are sufficient to account for the death of animals. Using large, medium-sized and particulate matter to produce embolism in dogs, these investigators were able to account for death by the rise of pulmonary arterial systolic and diastolic pressure with resultant right ventricular heart failure. Cardiac arrhythmias are known to accompany pulmonary embolism both clinically and in the experimental field. They consist of auricular flutter, auricular fibrillation and terminal ventricular fibrillation in animals<sup>24</sup> and are the end result of failure of the right ventricle. Sudden death from pulmonary embolism, even though the embolism is relatively small, is best explained by the same mechanism of cardiac arrhythmia, probably resulting in ventricular fibrillation.

The occasional patient encountered clinically in whom angina pectoris develops after an attack of pulmonary embolism and is relieved by glyceryl trinitrate, as in case 7, is cited<sup>12a</sup> as giving evidence in favor of a reflex on the coronary arteries. However, there are undoubtedly other factors which affect coronary blood flow, such as fall of arterial pressure, which usually is associated with an increase of heart rate. The rise of pressure in the right auricle also increases the pressure in the coronary sinus, and this increase decreases the pressure gradient in the coronary arteries. The third contributing factor is the decrease of blood flow to the muscle of the right ventricle since, as Katz, Jochim and Weinstein<sup>25</sup> pointed out and as Visscher<sup>26</sup> emphasized, the major portion (92 per cent) of the venous return from the right ventricular wall empties into the right ventricle via the thebesian veins. Thus increase of pressure in the right ventricle decreases appreciably the coronary flow to this side of the heart. All these factors combine to impair the function of the right ventricle. The combined effect of increased work of the right ventricle and decreased coronary blood flow may account for the angina pectoris without the necessity of postulating a pulmonocoronary reflex to account for it.

That anatomic changes of the myocardium occur after pulmonary embolism has been demonstrated in recent publications<sup>27</sup>. Those changes in the myocardium are not often demonstrable, as is illustrated by the finding of only 5 cases in a total of 30 cases in this somewhat selective series. The fact that in 4 of these 5 cases no significant obstruction was found in the coronary arteries to account for acute infarction suggests that another factor, probably shock, contributes a great deal to the decrease of coronary blood flow. As far as infarction in the right ventricle is concerned, the rise of right intraventricular pressure also has the effect of decreasing coronary blood flow by decreasing the pressure gradient in the coronary artery, as pointed out in the preceding paragraph. Blumgart, Schlesinger and Zoll<sup>28</sup> have called attention to the fact that shock seems to predispose to coronary arterial thrombosis, and this is illustrated by case 5 of the present series. That profound shock alone can account for acute myocardial infarction is demonstrated clearly by case 6. It is interesting to note that in this case the infarction was located in that portion of the posterior left ventricular wall supplied by the right coronary artery, and this was predominantly true in cases 1, 2 and 5 of the cases presented.

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27 Friedberg, C. K., and Horn, H. Acute Myocardial Infarction Not Due to Coronary Artery Occlusion, *J A M A* **112** 1675-1679 (April 29) 1939.

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On December 24, while walking about, he was seized with sudden weakness and vomiting but did not lose consciousness

When examined, one hour later, he showed moderate cyanosis, the extremities were cold, the skin was moist and the blood pressure was 80 mm of mercury systolic and 40 diastolic. The pulse rate was regular at 120, and the respiratory rate was 40. The patient complained of moderate substernal pain. Oxygen (100 per cent) was administered, and the patient gradually improved so that after ten hours the pulse rate was 110, the blood pressure 100 systolic and 70 diastolic, and the respiratory rate 28. The electrocardiogram taken on December 24 revealed exaggerated P waves in leads II and III, shallow inversion of the T wave in lead III, an inverted T wave in lead CR, and an abnormally positive T wave in the Wolferth lead (fig 9).

The patient improved after this episode, but on Jan 2, 1941 he had a gradual rise of temperature to 102 F with a concomitant rise of the pulse rate to 110 and of the respiratory rate to 30, during which time the pain in the right side of the chest returned. His condition again improved, and he was prepared for dismissal when, on January 8, while being bathed, he suddenly became weak and dyspneic, vomited, complained of pain in the lower anterior portion of the chest and died within an hour.

The anatomic diagnosis was (1) bilateral fatal pulmonary embolism with pulmonary infarction (source undetermined) and (2) hydrothorax on the right (400 cc).

The heart weighed 305 Gm. The right ventricle was dilated (grade 3), and the wall measured 5 mm in thickness. The coronary arteries were patent throughout, and the sclerosis was grade 1. Sections of the heart failed to reveal any regions of acute or healing infarction. In the inferior vena cava, a medium-sized clot was found lying loosely at the level of the renal vein but without attachment to the wall.

Case 8 well illustrates the diagnostic value of the electrocardiographic leads from the chest in pulmonary embolism. The leads from the limbs by themselves were of little value in corroborating the clinical impression of pulmonary embolism, although the exaggeration of P waves in leads II and III might be suggestive. However, the T waves in the CR<sub>2</sub> and Wolferth leads are the reverse of normal and under these circumstances are diagnostic of pulmonary embolism. It will be noted also that these changes take place, as in case 7, in the absence of demonstrable anatomic alterations of the myocardium.

#### GENERAL COMMENT

The role that reflex factors resulting from embolism in the pulmonary artery may play in the clinical picture of pulmonary embolism has received considerable comment in recent years. Some writers, particularly Leriche and de Takáts, have expressed the belief that in many cases the reflex factors play a major role and that, in fact, they are the cause of death in from 20 to 30 per cent of cases. These are cases in which at necropsy there are only small emboli in the pulmonary artery. Daly and his associates<sup>22</sup> demonstrated in dogs that a small but definite fall of the systemic arterial pressure accompanies a rise of the pulmonary arterial pressure, with a concomitant increase or decrease of the heart rate. A definite increase of the respiratory rate with embolism of the small pulmonary arterioles produced with particulate matter had been noted already, but this finding is difficult to translate into the clinical picture in which the embolizing clots are considerably larger. The reflex changes just mentioned disappear after the vagus nerves are sectioned. The observations by Scherf and Schonbrunner regarding the electrocardiographic changes in experimental pulmonary embolism seem insufficient alone to establish the occurrence of a pulmonocoronary reflex.

The recent observations by Megibow, Katz and Steinitz<sup>23</sup> concerning the dynamics of experimental pulmonary embolism again suggest that dynamic factors

<sup>22</sup> Daly, I. de B., Ludany, G., Todd, A., and Verney, E. B., Sensory Receptors in the Pulmonary Vascular Bed, *Quart J Exper Physiol* **27** 123-146, (Aug) 1937.

<sup>23</sup> Megibow, R. S., Katz, L. N., and Steinitz, F. S., Dynamic Changes in Experimental Pulmonary Embolism, *Surgery* **11** 19-32 (Jan) 1942.

# CLINICAL EFFECTIVENESS AND SAFETY OF A NEW SYNTHETIC ANALGESIC DRUG, DEMEROL

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NEW YORK

Since March 1941 I have had the opportunity to investigate a new synthetic analgesic drug, demerol,<sup>1</sup> for the treatment of pain due to a variety of medical and surgical conditions. A year's experience has definitely indicated its value as an analgesic agent, and it was therefore deemed advisable to report on its effectiveness, potency and safety. In addition, its pharmacologic action in man relative to a comparison with morphine will be considered briefly.

Eisleb and Schaumann<sup>2</sup> introduced the drug in 1939 in an effort to obtain a synthetic substitute for atropine. However, it was soon noted on pharmacologic grounds that in addition to a slight atropine-like action on all smooth muscle, the drug possessed the unexpected effect of a morphine-like response on the central nervous system. Extensive pharmacologic and toxicologic studies have since been reported by Duguid and Heathcote<sup>3</sup>, Schaumann<sup>4</sup>, Gruber, Hart and Gruber,<sup>5</sup> and Barlow<sup>6</sup>. With the exception of Gruber and his co-workers, who noted a spasmodic action of demerol on all smooth muscle, all investigators have reported an anti-spasmodic action attributable to a depression of the parasympathetic nerve endings and of smooth muscle directly. The former action resembled that of atropine but was not as marked, while the direct muscular depression was greater than that produced by papaverine. After careful experiments on animals and on human subjects, particularly on the latter, Barlow,<sup>7</sup> using the Hardy, Wolff and Goodell<sup>8</sup>

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1 The Alba Pharmaceutical Company, Inc., supplied us with the drug and with other aid in connection with this investigation.

2 Eisleb, O, and Schaumann, O. Dolantin, ein neuartiges Spasmolytikum und Analgetikum (Chemisches und Pharmakologisches), *Deutsche med Wchnschr* **65** 967 (June 16) 1939.

3 Duguid, A M E, and Heathcote, R St A. Pharmacological Action of Ethyl Methyl-phenylpiperidine Carboxylate, *Quart J Pharm & Pharmacol* **13** 318 (Oct-Dec) 1940.

4 Schaumann, O. Ueber eine neue Klasse von Verbindungen mit spasmolytischer und zentral analgetischer Wirksamkeit unter besonderer Berücksichtigung des 1-Methyl-4-Phenyl-Piperidine-4-Carbonsäure Athylesters (Dolantin), *Aich f exper Path u Pharmakol* **196** 109, 1940.

5 Gruber, C M, Hart, E R, and Gruber, C M, Jr. The Pharmacology and Toxicology of the Ethyl Ester of 1-Methyl-4-Phenyl-Piperidine-4-Carboxylic Acid (Demerol), *J Pharmacol & Exper Therap* **73** 319 (Nov) 1941.

6 Barlow, O W. Studies on Pharmacology of 1-Methyl-4-Phenylpiperidin-4-Carbonic Acid Ethylester (D-140, Demerol) II Pharmacology, Toxicology, and Addiction Liability, to be published.

7 Barlow, O W. Studies on the Pharmacology of 1-Methyl-4-Phenylpiperidine-4-Carbonic Acid Ethyl Ester (D-140, Demerol) I Analgesic Action, to be published.

8 Hardy, J D, Wolff, H G, and Goodell, H. Studies on Pain. A New Method for Measuring Pain Threshold, Observations on Spatial Summation of Pain, *J Clin Investigation* **19** 649, 1940.

Electrocardiographic tracings were not obtained in all the cases in this series, so that it is impossible to determine the incidence of various types of changes in the electrocardiograms Sokolow, Katz and Muscovitz<sup>29</sup> studied 50 cases of pulmonary embolism and noted only 5 with all of the changes delineated by McGinn and White However, in 36 cases some of the electrocardiographic features of pulmonary embolism were present and could be termed suggestive of pulmonary embolism In this regard Barnes<sup>30</sup> and Wood<sup>31</sup> directed attention to the value of the chest leads in the diagnosis of pulmonary embolism Cases 7 and 8 illustrate well the value of these leads, especially the Wolfarth lead

As pointed out previously, the anatomic changes of acute infarction of the myocardium are infrequent in patients dying of pulmonary embolism It is obvious, therefore, that the electrocardiographic changes known to indicate pulmonary embolism seldom if ever can be explained on that basis Cases are presented (7 and 8) in which the electrocardiograms were characteristic of pulmonary embolism but in which no demonstrable anatomic change of the myocardium was found after careful search Case 1 illustrates the electrocardiographic picture which may result if myocardial infarction occurs in the posterior portion of the right or the left ventricles after an attack of pulmonary embolism In general, the strain placed on the right ventricle by pulmonary embolism seems to be the dominant factor in the production of the electrocardiographic picture When shock is present a decrease of the coronary blood flow to the right side of the heart undoubtedly occurs In the right ventricle this factor plus strain is complicated by a decrease of coronary blood flow to the right ventricle, resulting from a fall of the pressure gradient in the arteries supplying it If these conditions are prolonged, marked dilatation occurs and scattered regions of acute infarction of the right ventricle can be demonstrated at times

#### SUMMARY

A study of the heart was made in cases in which pulmonary embolism occurred It is noted that the size of the heart in the surgical group of cases in which pulmonary embolism develops and the surgical group in which pulmonary embolism does not develop is essentially the same Since chronic valvular defects and disease of the pericardium were excluded as causes of cardiac enlargement, this evidence indicates that hypertension does not predispose to pulmonary embolism among surgical patients The heart was examined in 30 cases in which pulmonary embolism occurred, and evidence of acute infarction was found in 5 In 4 of these cases, no significant obstruction was found in the coronary arteries, but in the fifth case there was fresh coronary thrombosis One case in which there was prolonged shock is presented In this case there was acute infarction involving the posterior wall of the left ventricle, without coronary thrombosis The electrocardiographic differentiation of infarction of the posterior wall of the left ventricle and pulmonary embolism is illustrated and discussed, and the value of the chest leads in differentiating the two is stressed The mechanism of the production of electrocardiographic changes is discussed and a possible explanation for angina pectoris, which occasionally occurs in pulmonary embolism, is suggested

102 Second Avenue, S W

29 Sokolow, M , Katz, L N, and Muscovitz, A N The Electrocardiogram in Pulmonary Embolism, *Am Heart J* **19** 166-184 (Feb) 1940

30 Barnes, A R Electrocardiographic Patterns Their Diagnostic and Clinical Significance, Springfield, Ill., Charles C Thomas, Publisher, 1940

31 Wood, P Pulmonary Embolism Diagnosis by Chest Lead Electrocardiography, *Brit. Heart J* **3** 21-29 (Jan) 1941

Hospital, were utilized for this purpose. Demerol was given to any patient presenting pain regardless of its causation, type, severity or duration or the organ involved. The age and sex of the patient and accompanying conditions were not factors for selection. Consciousness and cooperativeness were the main considerations, since subjective responses were essential for evaluation of effectiveness and untoward reactions.

The scope of the investigation is presented in table 1. Of the 1,220 patients to whom demerol was administered, 1,119 were included in the final analysis. The others were discarded because they may have received other medication at the same time or because their mental state made it impossible to obtain adequate subjective data. There are 462 female and 657 male patients, ranging in age from 13 to 92 years. The records of 136 ambulatory patients<sup>21</sup> have been included only for a

TABLE 1—*Scope of the Investigation on Demerol*

		Number of Patients
Hospitalized patients	Females	462
	Males	657
	Total	1,119
Ambulatory patients		136
Age	13 to 92	
Surgical conditions	Postoperative	418
	Nonoperative	406
	Total	824
Medical conditions		406
Dose (parenteral and oral)	50 to 200 mg	
Patients receiving demerol	Parenterally only	436
	Orally only	300
	Parenterally and orally both	383
	Total	1,119
Period of administration of demerol, days		
7 or less		805
8 to 14		158
15 to 30		96
31 to 60		43
61 to 90		13
Over 90		4
Total		1,119
Doses administered to hospitalized patients	Parenteral	10,320
	Oral	10,581

comparative analysis with those of the hospitalized patients for untoward reactions. The effectiveness of demerol in this group will not be considered at the present time.

Several additional groups of patients have received demerol for purposes other than the relief of pain. Investigation is now in progress regarding the use of demerol (1) as a sedative or soporific, (2) in the treatment of bronchial asthma, (3) in the relief of the acute dyspnea of congestive heart failure, (4) in the treatment of addiction to opiates and (5) as an analgesic agent in obstetrics. Rovenstine and Batterman<sup>22</sup> are reporting on its use as a substitute for morphine as a pre-anesthetic agent.

21 Ambulatory patients were made available for study by Dr. Currier McEwen, Chief of the Arthritis Clinic, Dr. Robert P. Wallace, Chief of the Gastroenterology Clinic, Dr. Aaron Brown, Chief of the Asthma Clinic, and Dr. Rieva Rosh, Chief of the Radiation Clinic, all of the Third Medical Division (New York University), Bellevue Hospital.

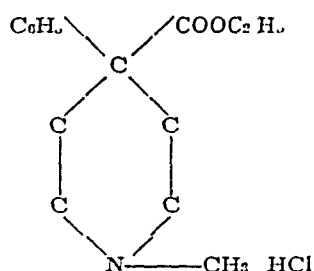
22 Rovenstine, E. A., and Batterman, R. C. The Utility of Demerol as a Substitute for the Opiates in Pre-Anesthetic Medication, Anesthesiology, to be published.



technic, concluded that in analgesic potency demerol was intermediate between codeine and morphine

Since 1939 numerous clinical reports have appeared attesting to the drug's effectiveness in relief of pain due to a variety of conditions. Its use for postoperative pain and other surgical conditions was described by Dolle,<sup>9</sup> Rosenthal,<sup>10</sup> Schafer,<sup>11</sup> Schlungbaum,<sup>12</sup> and Sostmann.<sup>13</sup> Medical conditions, including arthritic, neurologic and colicky pains of all organs and causations, were reported by Althoff,<sup>14</sup> Dietrich,<sup>15</sup> Klein,<sup>16</sup> Reisinger<sup>17</sup> and Heydner.<sup>18</sup> The consensus was that demerol<sup>19</sup> was a safe analgesic approximating the effectiveness of morphine for the relief of pain.

Demerol is 1-methyl-4-phenylpiperidine-4-carboxylic acid ethyl ester hydrochloride and has the following structural formula



It differs from morphine in that it is relatively simple and does not contain the phenolic and alcoholic hydroxyl groups attached to a phenanthrene nucleus to which the properties of morphine have been attributed. However, on close inspection of the morphine structure a piperidine ring can be made out if the ethenamine chain attached to the phenanthrene nucleus is rearranged. Atropine also possesses a piperidine ring, but this is included in the tropine nucleus.

#### SCOPE OF INVESTIGATION AND SELECTION OF PATIENTS

During the period of investigation, from March 1941 through April 1942, demerol was used in an effort to control or abolish the pain associated with a large variety of medical and surgical conditions. Patients admitted to the medical and surgical wards of the Third Medical Division<sup>20</sup> (New York University), Bellevue

9 Dolle, W. Dolantin, ein neues Spasmolyticum und Analgeticum in der Gynakologie, *Prakt. Arzt* **25** 113, 1940.

10 Rosenthal, H. Beobachtungen zur Bekämpfung des Wundschmerzes mit dem neuen Analgetikum, Dolantin, München med. Wchnschr. **86** 1079 (July 14) 1939.

11 Schafer, F. Schmerzbehandlung in der Chirurgie mit Dolantin, *Deutsche med. Wchnschr.* **65** 970 (June 16) 1939.

12 Schlungbaum, H. Schmerz Bekämpfung mit Dolantin, einem synthetisch hergestellten Spasmolytikum und Analgetikum, *Med. Klin.* **35** 1259 (Sept. 22) 1939.

13 Sostmann, H. E. Zur Ablosung des Morphins und seiner Abkommlinge in der Gynakologie durch Dolantin, *Med. Welt* **14** 325 (March 30) 1940.

14 Althoff, H. Klinische Erfahrungen mit Dolantin-Bayer, *Therap. d. Gegenw.* **6** 258, 1939.

15 Dietrich, H. Klinische Erfahrungen mit einem neuen synthetischen Spasmolytikum und Analgetikum, *Deutsche med. Wchnschr.* **65** 969 (June 16) 1939.

16 Klein, E. K. Erfahrungen mit Dolantin, einem Myotrop und Neurotrop wirkenden Spasmolytikum, München med. Wchnschr. **86** 1674 (Nov. 24) 1939.

17 Reisinger, F. Das neue Analgetikum und Spasmolyticum Dolantin, *Wien med. Wchnschr.* **90** 400, 1940.

18 Heydner, W. Erfahrung mit dem Spasmo-Analgetikum Dolantin bei Nervkranken, *Fortschr. d. Therap.* **16** 33, 1940.

19 Demerol was introduced in Europe as "eudolat" and was subsequently known on that continent and in South America as "dolantin."

20 Dr. William S. Tillett, Director of the Third Medical Division, and Dr. John H. Mulholland, Director of the Third Surgical Division, furnished clinical material for this study.

TABLE 2—Effectiveness of Demerol in Terms of Dose, Administered Both Parenterally and Orally, Regardless of Diagnosis or Severity of Pain

Dose, Mg	Effectiveness																	
	Administered Parenterally*						Administered Orally*											
	Complete		Moderate		Slight		Complete		Moderate		Slight		None					
	No	%	No	%	No	%	No	%	No	%	No	%	No	%				
	No of Trials†								No of Trials†									
50	83	56	67.4	19	22.9	6	7.2	2	2.4	235	128	54.4	48	20.4	32	13.6	27	11.5
75	222	182	81.9	29	13.0	7	3.1	1	1.8	39	18	46.1	11	28.2	7	17.9	3	7.7
100	643	569	88.4	54	8.4	9	1.4	11	1.7	431	284	65.9	103	23.9	21	4.9	23	5.3
150	40	34	85.0	4	10.0			2	5.0	14	6	42.9	8	57.1				
200	8	8	100							3	1		2					
Total	996	849	85.2	106	10.6	22	2.2	19	1.9	722	437	60.5	172	23.8	60	8.3	53	7.3

\* Different doses and methods of administration may have been used on the same patient

† Number of trials of demerol possible of evaluation

Demerol was used in the treatment of pain due to surgical conditions in 824 patients and to medical conditions in 406 patients. If a patient presented more than one type of pain at the same or at different times he was included for evaluation of effectiveness in the appropriate groups of diagnoses. For example, a patient may have been treated for pyloric spasm and therefore included in the medical group. However, if surgical intervention was performed on the same patient, he was also included under postoperative pain in the surgical group.

The drug <sup>23</sup> was administered in doses of 50 to 200 mg in a single dose or in repeated doses several times daily. Different doses or routes of administration may have been used in the same patient. It was thus given only parenterally (intramuscularly or subcutaneously) to 436 patients, only orally to 300 patients and by both methods at different times to 383 patients. The majority of the patients received the drug for less than one week, but in 60 patients it was possible to study its effects for over a month. Over ten thousand injections and a similar number of oral doses were administered to the hospitalized patients, 11 patients receiving more than 20,000 mg of the compound.

### RESULTS

After the oral administration of demerol an analgesic effect is apparent within twenty to sixty minutes, and after parenteral administration, within fifteen minutes. In either case the analgesia lasts from one to several hours, with an average duration of three hours. As in the case of other analgesics, the more severe the pain, the shorter the duration of action. Pain of visceral origin is relieved for longer periods than pain arising from skeletal or neurologic structures. The intensity and the duration of the effect, in contrast to those of morphine and codeine, were not influenced by the presence of anemia or advanced disease of the liver, kidneys or heart.

In evaluating the effectiveness of demerol several factors were taken into consideration. It must be emphasized that one is dealing with a symptomatic measure and not a specific cure. An analgesic agent offers only a means of controlling the pain, thus making the patient comfortable while the specific cause of his complaints is discovered and eradicated. This aspect is often overlooked, and when assessing an analgesic drug one finds, particularly if the medication is given only occasionally, that the patient may continue to have pain. On close questioning, however, one may discover that there was complete relief of pain for the duration of the drug's action, but when the effect is dissipated, the patient considers himself unrelieved. Therefore, the principal factors considered in my analysis were the degree and the duration of relief of pain, dependent on the type of pain, the dose of drug administered, the rapidity of dissipation of the drug from the body, and the psychologic makeup of the patient. The last is of prime importance, since much of my data is obtained by close questioning of the patient.

With this in mind the effectiveness of demerol was divided into four categories.

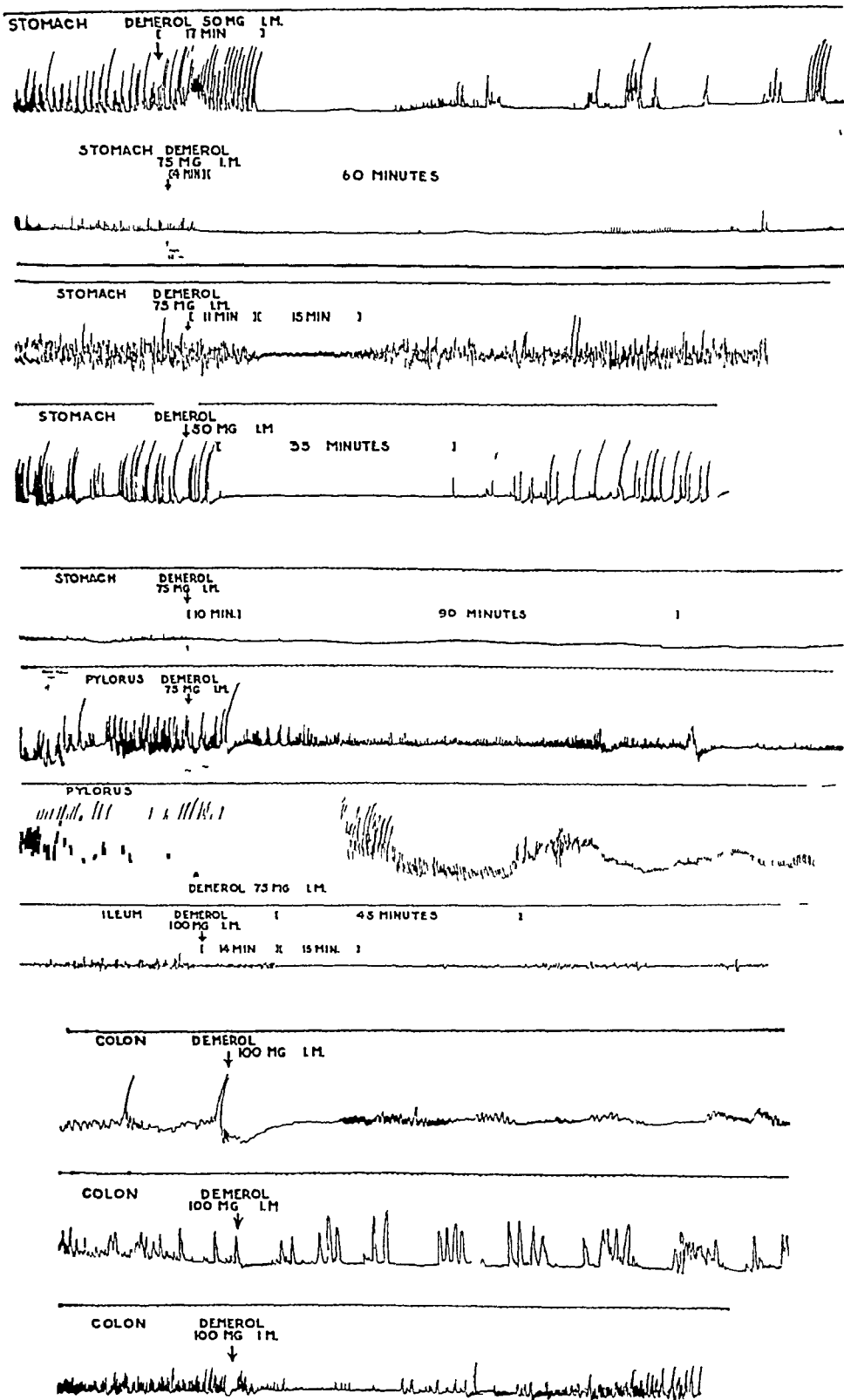
- 1 Complete control of pain, including complete relief of pain for three or more hours and almost complete relief of pain for several hours. In this group untoward reactions were minimal or entirely absent.

- 2 Moderate control of pain, including complete relief and almost complete relief of pain for under three hours, partial relief for three hours or more and relief as described in the first category if untoward reactions were disturbing and did not permit complete comfort.

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<sup>23</sup> Demerol was supplied in 50 mg tablets under the research number D-140 and in solution, research number S-140, either in an ampule or in a vial so that 1 cc was equivalent to 50 mg.

For all medical conditions demerol administered parenterally was completely effective in 80 per cent of the trials and moderately effective in an additional 15 per cent. Although in 76 per cent of the trials a moderately to completely satisfactory



Representative tracings made on 11 subjects after intubation studies with balloons in various portions of the gastrointestinal tract, showing the antispasmodic action of demerol administered parenterally

response was obtained with the orally administered preparation, the relief of pain is less rapid and less dramatic than after injection. By all methods of administra-

3 Slight control of pain, including partial relief for under three hours and relief as described in the first and the second category if untoward reactions were moderately severe

4 No control of pain, including failure to affect pain and relief as described in the first three categories if untoward reactions were severe

The effectiveness in terms of dose, both parenteral and oral, regardless of diagnosis, is summarized in table 2. With increasing dose a higher incidence of complete control of pain is obtained. For the average patient 100 mg of demerol is a satisfactory dose. Such a dose resulted in a good effect in 88 per cent of the trials after parenteral administration and 66 per cent after oral administration. The latter method of administration gives an effect equivalent to one obtained with 50 mg given intramuscularly. In many instances in which an opportunity presented itself for a comparison with morphine, it was apparent that 100 mg of demerol given intramuscularly was equivalent to 10 mg of morphine. However, the duration of action was not as long.

From table 3 it will be noted that regardless of causation and severity of the pain, completely satisfactory results were achieved in 85 per cent of the 997 trials in 881 of the patients to whom demerol was administered parenterally and in 60 per

TABLE 3—*Effectiveness of Demerol in Each Group of Patients Treated, Parenterally and Orally, Regardless of Dose*

Diagnosis	Method of Administration of Demerol	No of Patients	No of Trials	Effectiveness, Percentage of Patients			
				Complete	Moderate	Slight	None
Postoperative pain	Parenteral	362	386	93.0	4.1	1.5	1.5
	Oral	96	101	88.1	8.9		2.9
Nonoperative surgical conditions	Parenteral	265	317	81.4	14.8	2.5	1.2
	Oral	255	316	64.8	23.1	6.0	6.0
Medical conditions	Parenteral	254	293	79.5	14.6	2.7	3.0
	Oral	253	305	46.9	29.5	13.4	10.2
All diagnoses	Parenteral	881	996	85.2	10.6	2.2	1.9
	Oral	604	722	60.5	23.8	8.3	7.3

cent of the 722 trials in 604 patients to whom it was given orally. If the patients in whom the drug was moderately effective are included, satisfactory control of pain was achieved in 96 per cent and 84 per cent, respectively, with parenteral and oral routes of administration.

The most satisfactory results were obtained in the group of patients treated postoperatively. The postoperative course following major surgical procedures, such as laparotomy, thyroidectomy, mastectomy and herniorrhaphy, is well controlled, with a minimum of untoward reactions. Here more than in any other group of patients may the results be considered on an objective basis, since for the first twenty-four hours after operation the patient is still under the influence of the anesthetic, and one must rely entirely on direct observation. The immediate relief of restlessness, the rapidity with which the patient becomes comfortable and the minimal distress produced by the usual postoperative therapeutic procedures are all striking objective evidence for the effectiveness of demerol under such circumstances.

In the treatment of nonoperative surgical conditions the parenteral use of the drug was found to be effective for skeletal pain associated with fractures and metastatic malignant growths, arterial occlusions, impending gangrene, thrombophlebitis, pleuritic pain of fractured ribs and nonspecific pain associated with various malignant growths. Although the oral use of demerol is less effective in this group, the pain may be satisfactorily controlled if an appropriate dose is given.

if associated with other reactions. Even then it is well tolerated, particularly if a beneficial relief of pain occurs, so that the patient will continue to take the medication without difficulty. It is unassociated with any cerebellar dysfunction, since nystagmus and ataxia do not occur. As the only manifestation of toxicity it occurred in 6 per cent of the hospitalized patients after parenteral or oral administration and in 15 per cent of the ambulatory patients.

Severe reactions are rare and take the form of extreme weakness, pallor, syncope, profuse, cold and clammy perspiration, marked dizziness, nausea, and vomiting. This syndrome occurred after oral administration in 7 ambulatory and 2 hospitalized patients, the latter being semiambulatory. This type of reaction resembles the vasomotor collapse described by Weiss and co-workers,<sup>24</sup> noted after

TABLE 5—Incidence of Side Effects with Demerol

Side Effects	Hospitalized Patients				Ambulatory Patients	
	Parenteral Route		Oral Route		Oral Route	
	Percent- age of All Patients	Percent- age of Patients with Side Effects	Percent- age of All Patients	Percent- age of Patients with Side Effects	Percent age of All Patients	Percent- age of Patients with Side Effects
Dizziness	22.1	59.5	18.4	71.1	58.8	87.0
Nausea	8.4	22.6	6.1	19.7	25.7	38.0
Vomiting	3.8	10.4	1.5	5.8	11.8	17.4
Syncope			0.3	1.2	5.1	7.6
Weakness	0.1	0.3	0.6	2.3	10.3	15.2
Visual disturbance	0.4	1.0	0.7	2.9	3.7	5.4
Headache	0.4	1.0	1.3	5.2	5.9	8.7
Nervousness	0.1	0.3	0.6	2.3	2.2	3.3
Palpitation			0.1	0.6		
Anxiety	0.1	0.3	0.1	0.6		
Depression			0.1	0.6	1.5	2.2
Chilly feeling			0.1	0.6	1.5	2.2
Tremors . .	0.4	1.0			5.1	7.6
Disorientation	0.3	0.7				
Urinary difficulty	0.3	0.7				
Respiratory depression	0.3	0.7				
Hangover			0.3	1.2	1.5	2.2
Perspiration	20.3	54.7	9.6	37.0	20.6	30.4
Dryness of mouth	6.2	16.7	7.2	27.7	18.4	27.2
Euphoria	8.3	22.3	4.0	15.6	9.6	14.1
Warmth	0.8	2.1	0.9	3.5	8.8	13.0
Tinnitus			0.1	0.6		

administration of nitrites to normal subjects in the upright position. Since demerol possesses vasodilating properties, as demonstrated in experimental animals by studies of blood flow,<sup>25</sup> this response is probably related to an inability to maintain the circulation within compensatory levels when the patient is not recumbent. In this regard, if a patient while ambulatory notes the onset of the reaction, it may be aborted or decreased in severity and duration by the patient's assuming a recumbent position for fifteen to thirty minutes.

In contrast to morphine, urinary retention and respiratory depression occurred rarely with demerol. The latter effect was noted in 2 patients of the 774 receiving the drug parenterally. In both instances the respiratory depression was of short duration and responded readily to the usual stimulants. The first patient had

24 Weiss, S., Wilkins, R. W., and Haynes, F. W. Nature of Circulatory Collapse Induced by Sodium Nitrite, *J. Clin. Investigation* **16** 73, 1937.

25 Unpublished observations.

tion excellent results are obtained in pleuritic pain regardless of causation, pain in neurologic conditions, such as sciatica, tabes dorsalis and radiculitis, cardiovascular pain, such as that associated with a severe anginal syndrome and the distress of congestive heart failure, and visceral or colicky pain of biliary, renal and gastrointestinal origin. The last is of particular interest, since the antispasmodic action of demerol contributes to its analgesic properties. In 27 human subjects direct intubation studies with balloons of various portions of the gastrointestinal tract revealed an antispasmodic response with 50 to 100 mg administered intramuscularly in 23, or 84 per cent, of the subjects. Complete cessation or diminution of motility occurred usually within ten minutes and lasted from fifteen to over ninety minutes (figure). The effect did not appear to be as great as that following medication with atropine, but demerol possessed the same gradient of action as atropine on the stomach, the ileum and the colon in the order named.

#### TOXICITY

Demerol was found to be safe and with the exception of certain side effects is nontoxic in therapeutic doses. The incidence of side effects for hospitalized and for

TABLE 4—*Incidence of Side Effects of Demerol in Hospitalized Patients Treated Parenterally and Orally and in Ambulatory Patients Treated Orally*

Route of Administration	Sex	No of Patients	Patients with Side Effects		Patients with Significant* Side Effects	
			Number	Percentage	Number	Percentage
Parenteral (hospitalized patients)	Male	464	182	39.2	116	25.0
	Female	310	105	33.9	82	26.4
	Total	774	287	37.1	198	25.5
Oral (hospitalized patients)	Male	359	84	23.4	62	17.3
	Female	311	89	28.6	73	23.4
	Total	670	173	25.8	135	20.1
Oral (ambulatory patients)	Total	136	92	67.6	85	62.5

\* Excluding euphoria, perspiration, flushing of the face and dryness of the mouth

ambulatory patients is summarized in table 4. These side effects are usually insignificant, are of brief duration and do not as a rule inconvenience the patient to any appreciable degree. Their occurrence is unpredictable, since they may appear after the first dose or only occasionally after several doses. The sex, age and weight of the patient, the diagnosis and the accompanying conditions do not have any relation to the type, frequency and severity of the side effects. After prolonged administration they occur with less frequency, may decrease in their intensity or may subside completely. It is not unusual for a rapid tolerance to the unpleasant reactions to develop and yet the patient may obtain an equal or even better relief of the pain. This tolerance varies for the individual subject. Hospitalized patients may be free of any undesirable reactions within twenty-four to forty-eight hours, no matter how severe they were at the initial dose. On the other hand, mild and usually undisturbing reactions may occur with each dose in ambulatory patients for several weeks or months.

The incidence of the various side effects, significant or otherwise, for each treated group is presented in table 5. The dizziness is mild and is often described as a "feeling of being drunk," "lightheadedness," "floating on air" or "swelling of the head." In ambulatory patients this symptom may be disturbing, particularly

subside It is essential to emphasize the fact that demerol is merely a symptomatic measure and not a cure In patients with chronic pain, a single dose may result in alleviation of the pain for only two to four hours, at which time, if no further medication is given, the pain returns to its original intensity This may be overcome by administering the drug several times at definite intervals of three to four hours at which time a maximum and prolonged analgesic effect is usually achieved

The sedative effect is definite but not marked Restlessness is immediately relieved, and in the majority of instances after parenteral administration of large doses sleep may be induced This is of short duration, usually less than the period of analgesia, but when the drug is given at night, the effect may merge into natural and restful sleep which lasts for several hours The orally administered dose may not be effective for this purpose, and if a soporific effect is desired in addition to analgesia other somnifacients may be necessary In contrast to morphine and codeine, excitation is rarely if ever observed with demerol

In both the hospitalized and the ambulatory patients, who took the drug for many weeks and months, it was impossible to establish with any certainty that tolerance to the general analgesia occurs A few patients required an increased dose to obtain relief of pain However, the patients' conditions may have changed and the pain increased in severity In fact, in several of these patients it was possible to return to a smaller dose or to the original dose to achieve the same effect as that gained at the onset of therapy

Although tolerance may develop for the effect by which the threshold for cutaneous pain is raised, as demonstrated by Andrews,<sup>26</sup> and for the side reactions, we feel that the likelihood of its occurrence for general analgesia is remote

The question of addiction liability must be considered carefully in view of the drug's resemblance to morphine particularly in producing euphoria and in its ability to satisfy partially the "need" for opiates in patients already addicted By the term addiction is meant the development of physical dependence on a drug, so that on its withdrawal symptoms and signs indicative of its need become manifest On the other hand, habituation represents the psychic craving for a drug to maintain a state of well-being or to achieve a desired effect, such as euphoria, analgesia or sedation In the latter case withdrawal symptoms do not result when administration of the drug is discontinued

European observers<sup>27</sup> and recently Himmelsbach<sup>28</sup> have reported on the liability of addiction to demerol There is no question that the administration of demerol without restriction of dose to addicts or postaddicts will cause physical dependence on and abuse of the drug In my own patients receiving the drug in controlled doses for several weeks or months, there has been no instance of primary addiction However, in view of the present limited experience with the drug, the possibility of the occurrence of addiction after extended administration in patients with chronic illness has not been excluded The question requires further study and can be answered only by trial on patients who have not previously received opiates At the present time it can be stated that demerol may result in habituation In a few instances, because of the analgesic and sedative effect or the occurrence of euphoria,

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26 Andrews, H L The Development of Tolerance to Demerol, *J Pharmacol & Exper Therap* **75** 338, 1942

27 Kucher, I Zwei Falle von Dolantinsucht, *Klin Wchnschr* **19** 688 (July 6) 1942  
von Brucke, S Ueber Dolantinabusus und einen Fall von Dolantindelir, *Wien klin Wchnschr* **53** 854 (Oct 18) 1940

28 Himmelsbach, C K The Addiction Liability of Demerol-(1-Methyl-4-Phenyl-Piperidine-4-Carbonic Acid Ethyl Ester), *J Pharmacol & Exper Therap* **75** 64, 1942



advanced carcinoma of the esophagus, and the reaction developed after 100 mg of demerol was given in combination with 0.0004 mg of scopolamine hydrobromide for preanesthesia. The second patient was markedly debilitated with generalized arteriosclerosis and presented the respiratory depression after a dose of 100 mg of the drug, even though for the previous month repeated injections of the same dose had not produced any untoward effects. In several cases in which morphine had previously produced respiratory depression demerol was easily substituted without causing this reaction.

Prolonged use of demerol did not result in any alteration of the hemopoietic system or impairment of renal function. In a few ambulatory patients anorexia was a prominent complaint at the onset of therapy, but this soon subsided, with restoration of normal appetite. On the other hand, many patients noted an improvement of their appetite. Constipation, which occurs in practically every patient treated with opiates, never resulted from medication with demerol.

It is of particular interest to note the occurrence of euphoria. Although it is listed as a side effect, the state of well-being may be considered a desired therapeutic effect. It is not noted in more than 8 to 10 per cent, which is considerably lower than the 90 per cent reported by Barlow<sup>7</sup> for normal subjects. The presence of pain, other accompanying side effects and the hospital atmosphere may explain the difference in incidence.

Finally, the drug may be given without fear to patients receiving sulfonamide compounds, since they did not appear to affect the potency or the safety of demerol.

#### PHARMACOLOGIC STUDIES IN MAN

In addition to the gastrointestinal intubation studies mentioned previously, extensive pharmacologic studies in man were undertaken to evaluate the drug's safety and its other actions besides analgesia. The electrocardiogram and the basal metabolic rate remain unaltered. The blood pressure and the ventricular rate are unaffected in therapeutic doses except in those patients presenting syncope, in which case the blood pressure falls moderately and the rate decreases. Unlike morphine demerol does not change the size of the pupil, and the pupillary reflexes can still be elicited. It is of interest to note that the corneal reflex and the sensitivity of the cornea are abolished in approximately 80 per cent of subjects. Drowsiness and sleep occur with the larger doses usually after parenteral administration, are of short duration and are not followed by depression or confusion.

#### COMMENT

For centuries opiates have been the most effective drugs for the relief of pain. Although they possess many undesirable side effects and disadvantages, their potency is such that their use became mandatory when severe pain was present. It is therefore unfortunate that other analgesic drugs, notably the coal tar derivatives, were ineffective for this type of pain. This is of particular importance in the treatment of chronic conditions, in which the indiscriminate use of a potent narcotic usually leads to development of physical dependence on the drug. Demerol is the first drug which appears to be of value in those patients who ordinarily would have required opiates for relief. With rare exceptions the pain and restlessness of patients after operation are more than satisfactorily controlled. Visceral pain, such as peritoneal and pleuritic irritation, as well as colicky pains of all types, is immediately relieved, with a minimum of undesirable side reactions. Conditions associated with chronic pain are also greatly relieved and the patients made comfortable with an appropriate dose of demerol, or once any side effects, if initially present,

# EFFECTIVE RENAL BLOOD FLOW, GLOMERULAR FILTRATION RATE AND TUBULAR EXCRETORY MASS IN ARTERIAL HYPERTENSION

## II EFFECT OF SUPRADIAPHRAGMATIC SPLANCHNICECTOMY WITH LOWER DORSAL SYMPATHETIC GANGLIONECTOMY

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In a previous paper<sup>1</sup> we reported the results of the determination of effective renal blood flow, glomerular filtration rate and tubular excretory mass by the diodrast and inulin clearance methods in 20 patients with arterial hypertension. It was concluded that arterial hypertension is associated with renal ischemia and that the reduction of blood supply to the kidney shows a definite correlation with the severity of the disease, as indicated by the changes, in the eyegrounds, the degree of thickening of the systemic arterioles, the renal function and the elevation of systolic and diastolic blood pressures. While this previous paper was in press, the results of similar studies were published by other investigators<sup>2</sup> who also concluded that the rate of renal blood flow is decreased in most cases of hypertension.

The purpose of this paper is to report the results of the determination of effective renal blood flow, glomerular filtration rate and tubular excretory mass after supradiaphragmatic splanchnicectomy and lower dorsal sympathetic ganglionectomy in patients who had been studied preoperatively. Peet, Woods and Braden<sup>3</sup> reported the clinical results of this operation in the treatment of 350 patients with arterial hypertension and found that in 51.4 per cent the blood pressure was significantly reduced.

Several hypotheses have been advanced to explain why different operations on the sympathetic nervous system frequently cause a drop in blood pressure.

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1 Foa, P P, Woods, W W, Peet, M M, and Foa, N L. Effective Renal Blood Flow, Glomerular Filtration Rate and Tubular Excretory Mass in Arterial Hypertension, *Arch Int Med* **69** 822 (May) 1942, abstracted, *Am J Path* **17** 446 (May) 1941.

2 Friedman, M, Selzer, A, and Rosenblum, H. The Renal Blood Flow in Hypertension as Determined in Patients with Variable, with Early and with Long-Standing Hypertension, *J A M A* **117** 92 (July 12) 1941. Goldring, W, Chasis, H, Ranges, H A, and Smith, H W. Effective Renal Blood Flow in Subjects with Essential Hypertension, *J Clin Investigation* **20** 637 (Nov) 1941. Chasis, H, and Redish, J. Effective Renal Blood Flow in the Separate Kidneys of Subjects with Essential Hypertension, *ibid* **20** 655 (Nov) 1941.

3 Peet, M M, Woods, W W, and Braden, S. The Surgical Treatment of Hypertension, *J A M A* **115** 1875 (Nov 30) 1940.

desire for the drug was expressed. However, none of these patients experienced any untoward reaction on withdrawal of the drug.

For hospitalized patients the average therapeutic dose of demerol is 50 to 100 mg administered orally or parenterally. If this dose is unsatisfactory, it may be increased by increments of 25 mg until a desired effect is achieved or 200 mg is being administered. It is unlikely that higher doses would be necessary, since it is unusual for a patient not to respond to a dose under 150 mg. However, if analgesia is not obtained with a dose as high as 200 mg, the probability of the patient's responding to a higher dose is remote. Furthermore, it has been my experience that an equivalent dose of morphine is also unlikely to produce a greater effect in such a case. With severe and acute pain a dose of 100 mg may be repeated in one or two hours if necessary. If side effects occur with the average dose and continue to occur with the same severity on subsequent doses, they may be prevented or decreased by giving a smaller dose of 25 to 50 mg until a tolerance develops for the undesirable reactions. It is then possible to return to the larger dose for the analgesic effect.

The initial dose for the ambulatory patient should be 50 mg at intervals of four hours. The patient should be cautioned as to the possibility of the occurrence of dizziness and weakness and advised to assume a supine position if these are severe. These symptoms usually subside quickly and gradually become less disturbing if the medication is continued. The dose may be increased to 75 or 100 mg if necessary.

Demerol offers several advantages. Besides being synthetic and a potent analgesic, it is relatively free of any serious toxic manifestations. Its use for conditions previously responding only to morphine allows the latter drug to be reserved for use in refractory cases. Respiratory depression and urinary difficulty are rare following its use. The absence of disturbance of pupillary reflexes makes the drug particularly useful for head injuries and other intracranial conditions. In contrast to the opiates, it may be used without fear in patients with severe anemia, disease of the liver or kidneys or bronchial asthma. Its antispasmodic action makes the drug ideal for the treatment of severe colicky pain. Finally, its general analgesic effects can be elicited for weeks or months after intensive therapy without any appreciable tolerance developing. The high incidence of side effects in ambulatory patients and the rapid dissipation of the drug from the body are two minor disadvantages. The former is only of temporary importance, since the side effects subside with prolonged use, and the short duration of analgesia may be overcome by administering the drug more often.

#### CONCLUSION

Demerol, a new synthetic analgesic, was studied in 1,119 hospitalized patients and found to be potent, effective and safe for the relief of pain due to a variety of medical and surgical conditions. It could be used in patients who ordinarily would have required opiates for relief. Hospitalized patients are relatively free of serious side effects, but because of the high incidence of dizziness and the possibility of syncope the drug should be used with caution on ambulatory patients.

This investigation was carried out under the direction of Prof. Arthur C. DeGraff. Miss Anele C. Evaskitis, research nurse of the Department of Therapeutics, New York University College of Medicine, assisted me in the pharmacologic studies and in obtaining data on the patients receiving demerol.

based on the facts that at low plasma concentration diodrast is practically completely cleared in one passage of the plasma through the kidneys and that therefore diodrast clearance measures the flow of plasma through the active renal tissue. When the concentration of diodrast in the plasma is increased enough to saturate the kidneys, the excretion of this substance reaches a maximum. This is proportional to the amount of excretory tissue and, expressed in milligrams of iodine excreted per minute, is used as a measure of the tubular excretory mass ( $T_{mp}$ ). Inulin is excreted only by glomerular filtration and is not reabsorbed by the tubules. Its clearance is therefore a measure of the filtration rate.

The eyegrounds of every patient have been reexamined and regrouped according to the Keith-Wagener classification and by objective findings, such as hemorrhages, exudates and papilledema.

Blood pressure readings were always taken by the same observer and under uniform conditions. Briefly, the patient was reclining, the blood pressure was taken from the right arm, the diastolic pressure was read when the sound first became dull, since in patients with hypertension it is frequently impossible to determine sharply the disappearance of all sounds. The recommendations of the American Heart Association<sup>11</sup> were followed in all other respects.

The term "blood pressure on admission" (see tables) is used to denote the blood pressure measured when the patient was admitted to the hospital before the operation and also when he was readmitted for the postoperative examination after five or more months. The term "blood pressure during test" is used to denote the average of all the blood pressure readings obtained during each determination of inulin and diodrast clearances. Blood pressure readings were taken approximately every five minutes for about three hours.

In the comment which follows on the effect of splanchnicectomy on renal circulation, an increase or decrease of 20 or more mm of mercury systolic and 10 or more mm of mercury diastolic in "blood pressure during test" was considered a significant change. No change of less than 15 mm in mean blood pressure or of less than 10 mm in pulse pressure was considered significant. We feel that these differences are great enough to rule out the possibility of an error of determination. In evaluating clinical results, however, for which daily and weekly fluctuations of blood pressure must be taken into account, the criteria of Peet, Woods and Braden<sup>8</sup> were used and a change of 40 systolic and 15 diastolic or more was considered significant.

## RESULTS

Of the 20 patients reported on in our previous paper,<sup>1, 2</sup> (S M and D M) died before any postoperative examination could be made, and 3 (E J, N E and T S) did not return for reexamination. For 15 patients the tests were repeated in from two weeks to twelve months after the operation. Two patients (B E and N N) who were not included in the first series are included in the group used for this paper.

Table 1 contains the average results of the tests, which were made shortly after the patients, 15 in number, had recovered from the operation, and when they were about to be discharged. Patient L C, who returned for her first postoperative examination two months after the operation, is included in table 1.

Table 2 contains the average results obtained for those patients, 15 in number, who were studied in from five to twelve months after the operation. Thirteen of our patients had two postoperative examinations and are included in tables 1 and 2.<sup>12</sup>

11 Standardization of Blood Pressure Readings, Joint Recommendations of the American Heart Association and the Cardiac Society of Great Britain and Ireland, *Am Heart J* 18:95 (July) 1938.

12 The reader will notice that the average preoperative values are not the same in table 1 as in table 2 and that they also differ from the average preoperative values given in the preceding paper. This is due to the fact that in each table preoperative averages were computed only on those patients who were examined at the postoperative time under consideration and that not all the patients who were reexamined two weeks after operation had a later check-up, or vice versa. Moreover, not all the patients who were studied preoperatively had further studies, and 2 new patients not reported in our preceding paper are included in these tables.

According to one theory, the denervation of the adrenal glands, which is more or less extensively accomplished by most of the operations recommended, decreases the hyperepinephrinemia to which hypertension is attributed. A second hypothesis is that the operation dilates the vessels controlled by the resected nerves, thus creating a large vascular bed with decreased resistance in the splanchnic area. As a working hypothesis, Peet<sup>4</sup> suggested that his type of splanchnicectomy dilates the renal arterioles and increases the blood flow through the kidneys in patients with arterial hypertension, thus attacking directly what might be considered the primary cause of the disease. Finally, we wish to present in this paper the hypothesis that improvement in blood pressure following splanchnicectomy is due to an increased pulse pressure in the renal arterioles.

It has been shown that section of different parts of the sympathetic nervous system cannot prevent or cure hypertension produced experimentally by clamping the renal arteries.<sup>5</sup> This fact has often been used as an argument against the surgical treatment of hypertension. It should be emphasized, however, that whereas the interruption of nervous pathways cannot modify renal circulation obstructed by an irremovable metal clamp, it could remove an obstruction due to a reversible spastic contraction of the renal arterioles. Evidence that in certain circumstances renal circulation is controlled by the nervous system has been presented.<sup>6</sup> As a matter of fact, renal denervation has proved effective in preventing or curing other forms of experimental hypertension, such as the one due to oxalate nephritis,<sup>7</sup> or the one due to injection of kieselguhr (purified siliceous earth) into the renal artery.<sup>8</sup> According to Grimson,<sup>9</sup> complete sympathectomy prevents and cures hypertension due to resection of the carotid and aortic depressor nerves.

#### METHODS AND CRITERIA

Diodrast and inulin clearances have been determined, with the same technic and precautions as in the preoperative studies.<sup>1</sup> From these determinations effective renal blood flow, glomerular filtration rate and tubular excretory mass have been computed. The principles of these methods have been extensively discussed by Smith and his associates.<sup>10</sup> They are

4 Peet, M. M. Splanchnic Section for Hypertension. A Preliminary Report, Univ Hosp Bull, Ann Arbor **1** 17 (June) 1935.

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9 Grimson, K. S. The Sympathetic Nervous System in Neurogenic and Renal Hypertension, Arch Surg **43** 284 (Aug) 1941.

10 Smith, H. W., Goldring, W., and Chasis, H. The Measurement of the Tubular Excretory Mass, Effective Blood Flow and Filtration Rate in the Normal Human Kidney, J Clin Investigation **17** 263 (May) 1938.

TABLE 3—Blood Pressure, Effective Renal Blood Flow and Other Data on Patients with Arterial Hypertension

Patient	N	Age	Sex	Time	Blood Pressure on Admission, Mm Hg			Blood Pressure During Test, Mm Hg			Effective Renal Flow, Cc per Min	Filtration Rate, (Cin) Cc per Min	Tubular Excretion (Tm), Mg Iodine per Min	Ratio of Ratio of		Arterioles, Wall/Lumen	Lyegrounds		
					Pressure	Mean	Pulse	Pressure	Mean	Pulse				Clearance to Inulin	Clearance to Inulin		K	W*	Changes †
N N	26	M	Preop Postop 2 wk	260/160	210	100	199/141 143/117	170 130	58 26	111.1 56.61	18.6 5.67	25.2 13.92	12.2 26.3	1.41	1.168	III III IV	H, E, Sp, Sc H, E, Sp, Sc H, E, Ed		
A O	34	F	Preop Postop 2 wk Postop 6 mo	220/110	180	80	210/126 216/121 214/142	168 168 181	84 85 72	201.8 361.8 346.1					1.0194	1.0194	IV	H, E, Ed	
C D	42	F	Preop Postop 2 wk Postop 7 mo	214/142	178	72	219/127 228/125 206/119	173 176 158	92 103 87	250.9 551.2 512.2	45.8 78.2 59.6	27.83 18.9 17.44			1.755	1.755	III IV	E, Sp, Sc H, E, Ed	
W J	34	M	Preop Postop 6½ mo	199/118	158	81	171/119 124/90	145 107	52 34	433.6 139.1	87.9 158.3	37.7 55.16			1.399	1.399	III II	H, E, Sp H, E, Sp Sc	
F E	46	F	Preop Postop 2 wk Postop 12 mo	220/130	175	90	212/131 207/126 205/131	171 166 168	81 81 74	496.7 412.4 471.0	85.0 86.75 99.6	27.03 31.46 36.29	10.98 2.78 5.63	2.78 5.63	0.6012	0.6012	III III IV	Sp Sp Sp, Ed	
D C	51	M	Preop Postop 2 wk Postop 10 mo	208/129	168	80	118/87 187/132 172/122	102 160 147	31 55 50	506.7 647.3 624.1			17.7	26.76	0.9053	0.9053	III III II	Sp Sp Sc	
V P	37	M	Preop Postop 2 wk Postop 6 mo	185/129	157	56	184/133 180/128 141/100	159 154 120	51 52 41	528.8 653.2 616.3	83.1 106.4 80.0	26.68 26.04 23.49			0.7645	0.7645	III II	Sp Sc	
S M	40	F	Preop Postop 5 mo	156/104	130	52	157/105 124/86	131 104	52 38	613.0 353.0	61.4 79.45	15.41 31.5			0.7499	0.7499	III II	Sp, Sc Sp, Sc	
P J	36	M	Preop Postop 2 wk Postop 6 mo	210/170	205	70	187/127 210/157 212/142	155 183 177	57 53 70	649.8 486.0 565.8	73.2 113.0 89.4	19.4 38.75 27.39			0.8191	0.8191	III III	H, E, Sp Sp Sp, Sc	
S B	39	F	Preop Postop 2 wk Postop 7 mo	234/149	191	85	203/123 148/96 142/87	163 122 114	80 52 55	669.5 527.0 741.0	119.8 91.3 215.0	28.43 26.04 41.6	9.75 10.62 18.4	2.80 2.65 8.22	0.9011	0.9011	III II	Sp Sc	
W C	52	F	Preop Postop 2 wk Postop 7 mo	225/130	177	95	188/102 182/112 156/99	145 147 127	86 70 57	681.8 634.7 599.1	120.6 102.8 103.8	30.48 27.71 27.92	13.9 12.3 14.11	4.28 3.38 4.22	1.367	1.367	III III	Sp Sp Sp	
B P	46	M	Preop Postop 3 wk Postop 6½ mo	200/150	175	50	188/137 169/139 168/123	162 154 145	51 30 45	691.75 594.6 899.1	176.3 95.8 129.5	42.76 26.7 28.46	8.14 10.45 11.95	3.45 2.72 3.92	1.012	1.012	Normal	Normal	
G S	44	M	Preop Postop 2 wk	166/123	144	43	158/92 146/93	125 119	64 53	788.7 904.4	109.5 101.5	24.74 18.96	13.41 11.71	3.18 2.19	0.5709	0.5709	? III III	? Sp Sp	
O C	28	M	Preop Postop 1½ wk Postop 7 mo	200/120	160	80	148/106 147/102 122/87	127 124 104	42 45 35	804.0 615.8 662.3	125.8 88.0 171.3	25.93 25.0 40.62	18.6 19.5 12.45	1.051	1.051	Normal	Normal		
A A	42	F	Preop Postop 2 wk Postop 8½ mo	210/150	180	60	198/126 210/126 170/110	162 168 140	72 84 60	807.9 839.08 686.1	143.9 156.0 121.0	26.16 25.95 25.68			1.151	1.151	II	Sc	
H M	39	F	Preop Postop 2 wk Postop 7 mo	167/110	138	57	171/108 175/109 175/108	139 142 142	63 66 67	846.0 899.4 548.66	71.5 82.0 81.4	15.49 15.94 26.08			0.9914	0.9914	III III	Sp, Sc Sp, Sc	
L C	26	F	Preop Postop 2 mo Postop 8 mo	210/120	165	90	171/108 175/109 162/81	139 142 121	63 66 81	846.0 899.4 1088.5	71.5 82.0 140.95	15.49 15.94 22.27	13.41 11.71 19.4	3.18 2.19 4.25	0.5709	0.567	II	Sc Normal	
				178/114	146	64	175/108	142	67	548.66	81.4	26.08					Normal		
				190/110	150	80	130/72	98	53	1017.0	177.9	29.52	12.5	3.65			Normal		
				135/67	101	63				1087.0	296.5	41.74	12.58	5.24			Normal		

\* K W, the Keith Wagner classification of hypertensive patients based on the condition of the ocular fundus  
† I, hemorrhages, F, exudates, R, papilledema, Sp, angiospasm, Sc, sclerosis

TABLE 1—Averages of Data Obtained on Reexamination Approximately Two Weeks After Operation

	Group 1 Markedly Reduced Renal Blood Flow		Group 2 Moderately Reduced Renal Blood Flow		Total Average	
	Pre operative	Post- operative	Pre operative	Post- operative	Pre operative	Post- operative
Blood pressure, mm Hg						
Systolic and diastolic	203/133	190/124	176/111	165/111	186/118	173/115
Mean pressure	168	157	144	138	152	144
Pulse pressure	70	66	65	54	68	58
Effective renal blood flow, cc per min	346.9	418.4	781.0	728.6	647.41	632.41
Filtration rate ( $C_{in}$ ), cc plasma per min	58.1	69.3	120.5	112.46	101.31	99.2
Filtration fraction (FF), percentage	26.68	22.58	26.18	26.06	26.34	24.99
Tubular excretory mass (Tmd) in mg iodine per min			35.73	41.0	35.73	41.0
Ratio of diodrast clearance to excretory mass ( $C_D/Tmd$ )†			13.70	10.91	13.70	10.91
Ratio of inulin clearance to excretory mass ( $C_{in}/Tmd$ )			3.82	2.73	3.82	2.73
Arteriolar ratio, wall/lumen . . . . .	1.0405		0.9367		0.9783	
Eye grounds						
Keith Wagener classification						
Normal		0		3		3
Group I		0		0		0
Group II		0		1		1
Group III		2		3		7
Group IV		4		0		4
Objective findings						
Normal		0		3		3
Sclerosis only		0		1		1
Spasm only		2		1		
Spasm and sclerosis		0		3		3
Retinitis		4		1		5

†  $C_D$  Effective renal plasma flow (diodrast clearance)

TABLE 2—Averages of Data Obtained on Reexamination Five to Twelve Months After Operation

	Group 1 Markedly Reduced Renal Blood Flow		Group 2 Moderately Reduced Renal Blood Flow		Total Average	
	Pre operative	Post operative	Pre- operative	Post operative	Pre operative	Post operative
Blood pressure, mm Hg						
On admission						
Systolic and diastolic	229/131	172/111	212/137	159/103	217/135	163/106
Mean pressure	180	142	175	131	176	135
Pulse pressure	95	61	75	56	82	57
During test						
Systolic and diastolic	197/128	169/110	176/113	159/102	183/117	160/104
Mean pressure	163	140	145	131	150	132
Pulse pressure	68	59	63	57	66	56
Effective renal blood flow, cc per min	427.5	510.4	764.6	682.4	660.9	629.45
Filtration rate ( $C_{in}$ ), cc plasma per min	75.5	99.4	115.16	143.65	102.94	130.05
Filtration fraction (FF), percentage	29.81	33.09	25.15	33.00	27.37	33.03
Tubular excretory mass (Tmd) in mg iodine per min			35.96	35.05	35.96	35.05
Ratio of diodrast clearance to excretory mass ( $C_D/Tmd$ )			11.63	12.05	11.63	12.05
Ratio of inulin clearance to excretory mass ( $C_{in}/Tmd$ )			3.95	5.32	3.95	5.32
Arteriolar ratio, wall/lumen	1.1124		0.9323		1.0095	
Eye grounds						
Keith Wagener classification						
Normal	0	0	3	2	3	2
Group I	0	0	0	0	0	0
Group II	0	2	1	4	1	6
Group III	3	4	5	3	8	7
Group IV	3	0	0	0	3	0
Objective findings						
Normal	0	0	3	2	3	2
Sclerosis only	0	2	1	3	1	5
Spasm only	2	2	0	3	2	5
Spasm and sclerosis	0	0	4	0	4	0
Retinitis	4	2	1	1	5	3

The systolic and diastolic pressures "during the test" averaged 183 and 117 before the operation and dropped to an average of 160 and 104 five to twelve months after the operation. The average mean blood pressure "during the test" dropped from 150 to 132, and the pulse pressure, from 66 to 56. The average "blood pressure on admission," systolic and diastolic, dropped from 217 and 135 to 163 and 106, and the average pulse pressure, from 82 to 57.

The foregoing are the average data. If the results obtained for the individual patients are now examined (table 3), it is again observed that no permanent significant changes in blood pressure or renal blood flow were obtained within two weeks after the operation, but that within from five to twelve months after the operation in a good number of cases the blood pressure was reduced without any significant change in renal blood flow.

*"Blood Pressure on Admission"*—According to the standards arbitrarily established for evaluating clinical results, 8 of the 15 patients who were examined five or more months after the operation had a significant drop in "blood pressure on admission" (1 or more than 40 systolic and 15 diastolic) and 7 had no improvement. Of these 7, however, E J had a drop of 21 mm in diastolic pressure, B E a drop of 34 systolic and 27 diastolic and H M a drop of 32 systolic and 6 diastolic. The 8 patients whose blood pressures were improved had no change in renal blood flow. It is interesting to note that neither of the 2 patients whose renal blood flow increased had a reduction in blood pressure, in fact, 1 had an increase of 13 in mean pressure.

*"Blood Pressure During Test"*—Two weeks after the operation the "blood pressure during test" was reduced more than 20 mm systolic and 10 mm diastolic in 3 patients out of 15 examined at this time. Five to twelve months after the operation, however, the number of patients in whom the "blood pressure during test" was reduced 20 systolic and 10 diastolic had increased to 8 out of 15. The pulse pressure was reduced by 10 or more in 8 out of 15.

*Effective Renal Blood Flow*—Two weeks after the operation, the effective renal blood flow was unchanged in 7 patients and increased in 2 patients. However, it remained extremely low in both of them. A doubtfully significant change in renal blood flow was noted in 8 patients. These results were, however, temporary. Five to twelve months after the operation (table 4) the renal blood flow showed no significant change, returning to approximately the preoperative values in 13 of 15 patients.

*Filtration Fraction*—Two weeks after the operation, the filtration fraction was reduced in 6 patients, unchanged in 4 patients and increased in 3 patients. Five to twelve months after the operation the picture was again changed. The filtration fraction was increased in 8 patients, of whom 4 had had a decrease or no change in this fraction two weeks after the operation. In only 3 patients was a reduction in filtration fraction maintained for from five to twelve months after the operation. In 1 case the filtration fraction, which was found unchanged two weeks after the operation, was decreased ten months later. It may be said, therefore, that the changes in filtration fraction after operation are not uniform.

*Tubular Excretory Mass*—The tubular excretory mass, two weeks after the operation, was increased in 3 patients, unchanged in 1 patient and decreased in 2 patients. Five to twelve months after the operation, the results were approximately the same.

In our paper on preoperative studies<sup>1</sup> the patients were divided into two groups according to their effective renal blood flow, and it was pointed out that patients in group 1, with a lower renal blood flow, were more severely ill than patients in



Tables 3 and 4 contain data obtained on individual patients

The data show that, on the average, two weeks after the operation there was no significant change in blood pressure or in renal circulation, although there were minor temporary changes in individual patients. Five to twelve months after the operation systolic, diastolic and pulse pressures were reduced in a good percentage of cases, but these changes were not accompanied by significant changes in the renal blood flow. As will be discussed later, we feel that this is significant. It is also apparent from the tables that frequently the final results of the operation appear only after several months and that no definite conclusions can be drawn when there is a short period of postoperative observation.

Approximately two weeks after splachnicectomy (table 1) the effective renal blood flow averaged 647.41 cc per minute, as compared with 632.41 cc per minute in the same patients before the operation, a change which may be considered insignificant. The filtration rate ( $C_{in}$ ) and filtration fraction (FF) did not change significantly either, averaging respectively 101.31 and 26.34 before the operation

TABLE 4—*Relation Between Drop in Blood Pressure and Changes in Renal Blood Flow Five to Twelve Months After Operation*

Patient	Blood Pressure on Admission, Mm Hg		Postoperative Renal Blood Flow as Compared to Preoperative
	Preoperative	Postoperative	
	Group 1		
A O	220/140	214/143	Increased
C D	250/120	199/118	Increased
W J	200/130	125/ 93	Unchanged
F E	220/130	208/128	Unchanged
D O	190/120	185/129	Doubtfully increased
V P	245/145	156/104	Unchanged
	Group 2		
S M	185/140	126/ 89	Decreased
E J	240/170	234/149	Unchanged
S B	225/130	142/ 90	Unchanged
W C	230/130	160/ 97	Unchanged
B E	200/150	166/123	Doubtfully increased
O C	210/150	120/ 90	Unchanged
A A	215/135	167/110	Unchanged
H M	210/120	178/114	Doubtfully decreased
L C	190/110	135/ 67	Unchanged

and 99.2 and 24.99 two weeks after the operation. The tubular excretory mass ( $Tm_D$ ) increased from 35.73 to 41.0, and accordingly the blood flow and filtration rate per unit of tubular excretory mass ( $C_D/Tm_D$  and  $C_{in}/Tm_D$ ) decreased from 13.7 to 10.91 and from 3.82 to 2.73 respectively. The average systolic and diastolic "blood pressures during the test" were 186 and 118 before the operation and 173 and 115 two weeks after. The average mean blood pressure was 152 before and 144 after, and the average pulse pressure dropped from 68 to 58.

Five to twelve months after splachnicectomy (table 2) the effective renal blood flow averaged 629.45 cc per minute, as compared with 660.9 cc per minute in the same patients before the operation, which is not a significant change. The average filtration rate rose from 102.94 cc per minute to 130.05 cc per minute, and accordingly the average filtration fraction increased from 27.37 to 33.03 per cent. The tubular excretory mass remained relatively unchanged, averaging 35.96 before the operation and 35.05 after it. The blood flow per unit of tubular excretory mass ( $C_D/Tm_D$ ) did not change significantly, being 11.63 before the operation and 12.05 after it. The filtration rate per unit of tubular excretory mass ( $C_{in}/Tm_D$ ) rose from 3.95 to 5.32.

the most common and found that it decreased immediately after partial constriction of the renal artery but that it returned to previous levels after a few minutes. They also found that the blood flow must be reduced by about two thirds to prevent its return to normal levels. Corcoran and Page<sup>16</sup> reported similar results. Alpert and Thomas<sup>17</sup> found that dogs with long-standing hypertension may have normal renal blood flow. Finally, Friedman, Sugarman and Selzer<sup>18</sup> recently published evidence showing that renal ischemia is probably a phenomenon secondary to hypertension. This evidence suggests that reduced blood flow through the kidneys per se is not the primary cause of experimental hypertension, since the hypertension persists in the face of a blood flow which has returned to normal. The only evidence contrary to this hypothesis is the observation of Mansfield and his associates<sup>19</sup> and of Cerqua and Samaan<sup>20</sup>. They increased the renal blood supply by pexis of spleen or omentum to the decapsulated kidney and obtained long-lasting reduction of blood pressure in hypertensive dogs. The reduction lasted until the newly formed collateral circulation was interrupted. This procedure, however, was entirely unsuccessful in relieving hypertension in man.<sup>21</sup>

The observations presented here on renal blood flow in man following supra-diaphragmatic splanchnicectomy and sympathetic ganglionectomy are consistent with the hypothesis that some factor other than renal ischemia is the primary cause of hypertension. This is borne out by the fact that there was no increase in effective renal blood flow in those patients whose blood pressure was definitely and persistently reduced by the operation. Two other changes in the dynamics of renal circulation suggest themselves as possible causes for the reduction in blood pressure.

1. The same amount of blood flows through the renal tissue after operation but is distributed more uniformly. We stated in our preceding paper<sup>1</sup> that hypertension might be due to "Irregular distribution of blood to the renal tissue with marked ischemia in one part of the kidney and comparatively normal circulation in other parts." It is conceivable that such ischemic parts might produce an amount of vasoconstrictor substance (? angiotonin) sufficient to produce hypertension. If after operation there were a better distribution of blood to the renal tissue, the tubular excretory mass would be increased, since diodrast would be carried by the blood to a larger number of nephrons. The results of the investigation reported here do not corroborate this hypothesis, because, as has been pointed out,

16 Corcoran, A. C., and Page, I. H. Renal Blood Flow in Experimental Hypertension Due to Constriction of the Renal Artery, *Am J Physiol* **133** P 249 (June) 1941.

17 Alpert, L. K., and Thomas, C. B. Renal Function in Hypertensive Dogs, *Bull Johns Hopkins Hosp* **66** 407 (June) 1940.

18 Friedman, M., Sugarman, H., and Selzer, A. The Relationship of Renal Blood Pressure and Blood Flow to the Production of Experimental Hypertension, *Am J Physiol* **134** 493 (Oct) 1941.

19 Mansfield, J. S., Weeks, D. M., Steiner, A., and Victor, J. Reduction of Experimental Renal Hypertension by Pexis of Spleen or Omentum on the Kidney, *Proc Soc Exper Biol & Med* **40** 708 (April) 1939.

20 Cerqua, S., and Samaan, A. Cure of Experimental Renal Hypertension, *Clin Sci* **4** 113 (Dec) 1939.

21 Abram, P., Ishii, M., and Wallich, R. Essai de traitement de l'hypertension artérielle d'origine renale par la revascularisation chirurgicale du rein (nephro-omentopexie), *Presse med* **47** 137 (Jan) 1939. Goldberg, S., Rodbard, S., and Katz, L. N. Increased Collateral Blood Supply to the Kidney in Renal Hypertension, *Surgery* **7** 869 (June) 1940. Bruger, M., and Carter, R. F. Nephro-Omentopexy and Nephromyopexy in the Treatment of Arterial Hypertension, *Ann Surg* **113** 381 (March) 1941.

group 2, who had a relatively higher renal blood flow. The average wall/lumen ratio of the systemic arterioles was 1.241 in group 1 and 1.009 in group 2, showing a greater organic thickening of the arteriolar wall in the patients of group 1 than in those of group 2. This grouping has proved to be of prognostic value. Seven of the 12 patients in group 1 had malignant hypertension, and 4 died (N. N., S. M. A. O. and D. M.). A fifth (E. J.) left the hospital in extremely poor condition, and it has been impossible to communicate with him. Only 2 (W. J. and V. P.) had a persistent drop in blood pressure of 40 systolic and 15 diastolic. One did not return for reexamination, and the other 3 had a drop in blood pressure which is probably significant although not sufficient to meet our arbitrary standards.

#### COMMENT

The effect of sympathectomy on the renal circulation of patients with essential hypertension has been reported recently by other authors.<sup>13</sup> They have concluded that sympathectomy does not modify the renal circulation. My associates and I must disagree with this conclusion for two reasons. First, the postoperative observation period was too short. It has been pointed out in a preceding paragraph that not infrequently the immediate effects of operation differ considerably from those observed several months later. Second, in the cases presented by Corcoran and Page<sup>13b</sup> and by Selzer and Friedman<sup>13c</sup> the blood pressure was not significantly reduced during the short period of postoperative observation. We feel that a drop in blood pressure is all important in reaching a conclusion as to the effects of the operation on the renal circulatory system. If no reduction of the blood pressure is obtained, possibly because the organic changes in the systemic arterioles are too far advanced to be reversible, one does not expect any change in the arterioles of the kidney by interruption of the vasoconstrictor fibers.

Our results indicate that bilateral supradiaphragmatic splanchnicectomy with lower dorsal sympathectomy does not significantly change the rate of effective renal blood flow or the tubular excretory mass of patients with arterial hypertension, irrespective of the effect on the blood pressure. The question arises whether "renal ischemia" can be considered the primary cause of hypertension in man. It may be that the ischemia of the kidneys is simply another aspect of the generalized arteriolar disease. Ever since Goldblatt first produced experimental hypertension by reducing the lumens of the renal arteries, it has been customary to refer to this type of hypertension as "hypertension due to renal ischemia." If the generally accepted meaning of the word ischemia, which is "reduced blood supply," is used, it becomes doubtful whether it indicates the condition in the kidneys of Goldblatt animals. In these animals the renal blood flow is not necessarily reduced once hypertension becomes established, because the increase in aortic pressure may compensate for the narrowing of the renal artery. As a matter of fact, Mann, Herrick, Essex and Baldes<sup>14</sup> have shown that the lumen of an artery must be greatly reduced before a significant reduction in blood flow can be obtained. Schroeder and Steele<sup>15</sup> measured the renal blood flow with a

13 (a) Alving, A. S., Adams, W., Grimson, K. S., Scott, C., and Sandiford, I. Effect of Bilateral Paravertebral Sympathectomy on the Cardiorenal System in Essential Hypertension, *Proc Inst Med Chicago* **13** 306 (Feb 15) 1941. (b) Corcoran, A. C., and Page, I. H. Renal Blood Flow and Sympathectomy in Hypertension, *Arch Surg* **42** 1072 (June) 1941. (c) Selzer, A., and Friedman, M. Effect of Bilateral Splanchnicectomy upon Renal Blood Flow in Hypertension, *Proc Soc Exper Biol & Med* **48** 429 (Nov) 1941.

14 Mann, F. C., Herrick, J. F., Essex, H. E., and Baldes, E. J. The Effect on the Blood Flow of Decreasing the Lumen of a Blood Vessel, *Surgery* **4** 249 (Aug) 1938.

15 Schroeder, H. A., and Steele, J. M. The Behavior of Renal Blood Flow After Partial Constriction of the Renal Artery, *J Exper Med* **72** 707 (Dec) 1940.

it is apparent how splanchnicectomy can modify the renal circulation by increasing the pulse pressure within the kidney, even though the rate of effective renal blood flow is not increased

The increase in filtration fraction which was found in 8 of 15 patients five to twelve months after the operation (tables 2 and 3) suggests that arteriolar dilatation may have occurred in the afferent glomerular arteriole, thus increasing the intraglomerular pressure. It was formerly believed by Smith and his associates<sup>29</sup> that the efferent arteriole plays a dominant role in controlling the rate of glomerular filtration. On the other hand, Lampert<sup>30</sup> has recently indicated that the dominant role may be played by the afferent arteriole. Our evidence indicates that both arterioles are probably important in the regulation of glomerular pressure.

Dilatation of the arterioles with concurrent changes in pulse pressure can, of course, occur only when the constriction is due to a reversible spasm which can be removed by an operative procedure, and not when it is due to sclerosis or hypertrophy of the wall. This is borne out by the fact that the best results following operation were obtained in the patients who preoperatively had the greatest degree of vasomotility and the least organic thickening of the systemic arterioles. In evaluating organic arteriolar damage, the measurement of effective renal blood flow and of the wall/lumen ratio of the systemic arterioles in this limited number of patients proved to be at least as valuable as the observation of the eyegrounds or the determinations of urea clearance and urine concentration. Further studies, on a larger number of patients, are needed to decide whether or not the determination of renal blood flow and the measurement of the wall/lumen ratio of the arterioles in biopsy specimens of muscle should be added to the routine preoperative studies of patients with arterial hypertension.

It is fully realized that the conclusions arrived at here are based on the measurement of the blood flow to the renal excretory tissue alone. The total renal blood flow cannot be measured by diodast clearance, since the blood to the connective tissue is not cleared<sup>31</sup>. It seems unlikely, however, that the connective tissue could play an important role in the production of hypertension.

#### SUMMARY

Diodast and inulin clearances were used to measure the effective renal blood flow and filtration rate in 17 patients with arterial hypertension. Measurements were made before bilateral supradiaphragmatic splanchnicectomy with lower dorsal sympathetic ganglionectomy and from two weeks to twelve months after the operation. The results indicate that the operation did not change the renal blood flow significantly, even when the blood pressure was reduced. There was a reduction of blood pressure in 8 patients. Constancy of renal blood flow combined with reduced blood pressure suggests decreased vascular resistance and intrarenal arteriolar vasodilatation, with a resultant increase in pulse pressure within the kidney.

The patients with the highest effective renal blood flow, the greatest vasomotility and the least thickening of the systemic arterioles received the most benefit from the operation. It is suggested that the determination of effective renal blood flow

29 Footnote 2. Smith, Goldring and Chasis<sup>10</sup>

30 Lampert, H. The Relative Changes in Afferent and Efferent Arteriolar Resistance in the Normal Human Kidney, *J Clin Investigation* **20** 545 (Sept.) 1941

31 Smith, H. W. Note on the Interpretation of Clearance Methods in the Diseased Kidney, *J Clin Investigation* **20** 631 (Nov.) 1941

tubular excretory mass was increased in only 3 of our patients, 2 of whom did not have a drop in blood pressure

2 The pulse pressure within the kidney is increased by the operation, and consequently the diffusion of a vasoconstrictor substance from the renal cells into the blood stream is prevented. The hypothesis that a decreased pulse pressure rather than a decreased renal blood flow might be the primary cause of hypertension has been suggested by Corcoran and Page<sup>22</sup>. Kohlstaedt and Page<sup>23</sup> have shown that when an isolated kidney is perfused with a reduced blood flow no angiotonin is liberated unless the pulse pressure is also reduced. Organs perfused with continuous flow become edematous, and the normal permeability of their cells is altered<sup>24</sup>. It is therefore conceivable that if the pulse pressure in the kidney in human hypertension were reduced the renal cells might allow the diffusion of a vasoconstrictor substance into the blood, producing increased systemic blood pressure.

The fact that in many patients the rate of effective renal blood flow is maintained after operation despite a reduction in blood pressure indicates that the resistance of the renal vessels is probably reduced and that therefore the renal arterioles may be dilated. What would be the effect of this dilatation on the pulse pressure within the renal arterioles? In order to answer this question the investigator must first understand the changes in pulse pressure within the arterial system as the vessels diminish in caliber from the heart to the capillary bed. Pulse pressure is at its maximum in the left ventricle and aorta, and as the arteries diminish in caliber the pulse pressure decreases, until it disappears in the capillaries and veins. It has been shown that the pulse pressure is diminished below the site of a constriction in an artery, such as coarctation of the aorta<sup>25</sup>. It can be assumed, therefore, that the pulse pressure is decreased in the constricted arterioles of the kidney in hypertensive patients. If these constricted arterioles are dilated by the interruption of vasoconstrictor impulses, it follows that the pulse pressure must be increased.

It would seem to be a contradiction that in most of the patients included in this study the brachial pulse pressure, which was high before operation, is decreased postoperatively, whereas the pulse pressure in the renal arterioles is increased. This apparent contradiction, however, is easily understood when one realizes that the preoperative high pulse pressure in the brachial artery was due to increased peripheral resistance. (For a more extensive discussion, see Bradley and Parker,<sup>26</sup> Wilkins and Duncan<sup>27</sup> and Wiggers<sup>28</sup>). If the peripheral resistance is reduced by removal of vasospasm, the pulse pressure in the brachial artery decreases, whereas it increases in the peripheral arterioles, which have become dilated. Thus

22 Corcoran, A. C., and Page, I. H. Renal Aspects of Experimental and Clinical Hypertension, *J. Lab. & Clin. Med.* **26** 1713 (Aug.) 1941.

23 Kohlstaedt, K. G., and Page, I. H. Production of Renin by Constricting the Renal Artery of an Isolated Kidney Perfused with Blood, *Proc. Soc. Exper. Biol. & Med.* **43** 136 (Jan.) 1940.

24 Parsons, R. J., and McMaster, P. D. The Effect of the Pulse upon the Formation and Flow of Lymph, *J. Exper. Med.* **68** 353 (Sept.) 1938.

25 Steele, J. M. Evidence for General Distribution of Peripheral Resistance in Coarctation of the Aorta. Report of Three Cases, *J. Clin. Investigation* **20** 473 (Sept.) 1941.

26 Bradley, S. E., and Parker, B. The Hemodynamic Effects of Angiotonin in Normal Man, *J. Clin. Investigation* **20** 715 (Nov.) 1941.

27 Wilkins, R. W., and Duncan, C. N. The Nature of the Arterial Hypertension Produced in Normal Subjects by the Administration of Angiotonin, *J. Clin. Investigation* **20** 721 (Nov.) 1941.

28 Wiggers, C. J. Basic Hemodynamic Principles Essential to Interpretation of Cardiovascular Disorders, *Bull. New York Acad. Med.* **18** 3 (Jan.) 1942.

DR GEORGE E WAKERLIN, Chicago It is worth while to point out that there has been experimental work done on the hypertensive dog to show that a reduction in renal blood flow is not necessary for the production of experimental renal hypertension by constriction of the renal arteries. Usually there is a reduction in renal blood flow in these dogs, but it is not a necessary concomitant of experimental renal hypertension, since in some dogs hypertension develops without any reduction in renal blood flow.

I agree with Dr Lamport that it still has to be demonstrated that a reduction in renal pulse pressure has any relation to the pathogenesis of experimental renal hypertension or clinical hypertension. If a reduction in pulse pressure does play a role, it must act through some chemical mechanism whereby the pressor substance, whatever that may be, is released from the kidney of the patient with essential hypertension.

It is well to emphasize that bilateral splanchnicectomy in the normal dog or human being results in only a temporary reduction in blood pressure. Dr Foa and his group reported that 50 per cent of their patients showed a reduction in blood pressure at the end of six or twelve months. That is not a long enough time for observation. A minimum period of three years is necessary before results of this sort can be reported as representing positive reductions in blood pressure.

If one examines the vast amount of data concerning the effect of splanchnicectomy on human beings with essential hypertension, one finds that after five years not more than 5 per cent of the patients continue to show a reduction in blood pressure. I am inclined to think that this 5 per cent represents a specific group within the genus of essential hypertension. There undoubtedly are various types of essential hypertension, and I do not feel that bilateral splanchnicectomy is indicated for essential hypertension until such time as we can determine whether the patient is a member of this special group of 5 per cent or one of the 95 per cent.

DR PIERO FOÀ, Ann Arbor, Mich. The figures that we have given are group figures, all individual figures were corrected for the average normal body surface of 1.73 square meters. The tubular mass was determined for every patient, and the results indicate that the blood flow is reduced in hypertensive persons also in relation to the mass of their kidneys.

We have presented the hypothesis of the pulse pressure as pure speculation. Unfortunately, there is no means of measuring directly the blood flow or the pulse pressure within the human kidneys, and we have to rely on indirect methods.

No vasomotor tonus seems to exist in normal kidneys. However, abnormal vasoconstrictor stimuli might be present in hypertensive patients.

Dr Freund stated that the operation is devastating. It certainly is severe, but I do not believe we can call an operation devastating when the patient can leave the hospital and gradually resume his normal activities after only two weeks, and when the average mortality is about 3 per cent.

I agree that some of the tests of renal function, such as determinations of urea clearance, nonprotein nitrogen and urea concentration, are fallacious. Hypertension can be present when renal function is perfectly normal. For this reason we believe that a test of renal circulation, such as the measurement of the blood flow, would tell more about a vascular disease than the aforementioned excretory tests.

The results of renal biopsy are undoubtedly very interesting. We have just completed the study of 350 muscle biopsies in patients who have been followed up to seven years after the operation and have found that there is a striking correlation between the degree of arteriosclerosis and the results of the operation. The biopsy of muscle might be just as good as a biopsy of the kidney and much easier to perform.

Dr Wakerlin also objected that the hypothesis of the pulse pressure is purely speculative. I have already answered that objection.

He also stated that splanchnicectomy does not reduce hypertension in Goldblatt dogs. This is to be expected, since the silver clamp on the renal artery cannot be removed by splanchnicectomy. In hypertensive patients, however, the silver clamp is represented by a spasm of the renal arterioles, which can conceivably be relaxed by interruption of the neural pathways carrying vasoconstrictor stimuli.

Only the 22 patients in whom renal blood flow has been studied have been followed for from six to twelve months. A larger series, of 350 consecutive patients, has been followed for periods up to seven years, 50 per cent of them had a significant reduction in blood pressure. The patients were unselected.

and the measurement of the wall/lumen ratio of the systemic arterioles in biopsy specimens of muscle might prove to be valuable in the preoperative study of patients with arterial hypertension

Our results are consistent with the hypothesis that reduced intrarenal pulse pressure, and not renal ischemia, is a causal factor in human hypertension

The Winthrop Chemical Company, Inc., supplied the diodrast

### ABSTRACT OF DISCUSSION

DR HAROLD LAMPORT, New York This paper is especially interesting because it shows the value of hemodynamic considerations in studying hypertension and the application to it of various therapies

Biopsy of muscle may well become a useful adjunct to hemodynamic studies It is also likely that the total renal excretory mass may be a good measure of the prospective usefulness in individual cases of splanchnicectomy along with other therapies

The role of the renal nerves is still not clear The observations of Smith's group, and of Glaskell, as well as my own observations, have shown that in the kidney of the quadruped there is not a constant vasomotor tone However, whether this is true of man is not known, and it is possible that man, being a biped, is different, so that in him the renal nerves may be continuously functional The renal-hypertensive mechanism Dr Foa has suggested may for that reason be of significance despite the negative animal experiments

The speculation concerning the relationship of the renal vasomotor nerves to the transmission of the pulse pressure through the blood vessels of the kidney is challenging While recognizing the intuitive appeal of Dr Foa's view that preganglionic interruption of the renal nerves may improve nutrition of the kidney by increasing its internal pulse pressure, like Dr Foà I am aware that scientific proof of this hypothesis has not yet been forthcoming

It must be remembered that when the blood pressure is much elevated in hypertension the pulse pressure is large, and when the blood pressure declines after successful therapy the systemic pulse pressure also diminishes Now, if at the same time that the pulse pressure falls systematically the renal arterioles dilate, there is an opposing factor On the one hand, the systemic pulse pressure is smaller, so that if the arterioles had remained constricted there should be a smaller internal pulse pressure in the kidneys But, on the other hand, the effect of arteriolar dilatation alone is to increase intrarenal pulse pressure by improving transmission of systemic pulse pressure When we have two such opposing tendencies, it is impossible to evaluate them without a quantitative estimate of their relative sizes Unfortunately, I do not know of any pertinent data

DR HUGO A FREUND, Detroit As clinicians we all agree that it is desirable to know as much as possible about the condition of a patient before subjecting him to as serious and at times as devastating an operation as a splanchnicectomy or any of the other types of operation that have been advised in the various clinics in this country

Patients frequently ask, "Do you think an operation will benefit me?" Because of the favorable results that I have seen in a number of carefully selected cases, and particularly because Dr Foa has said that only 50 per cent of his patients have shown favorable results, my associates and I have diligently searched for specific criteria which might form a better basis for selection of patients for operation in whom a favorable outcome might be expected

It seems to me that the proper basis for the selection for operation of such patients would be an accurate knowledge of the pathologic state of the kidneys Functional tests of the kidneys, as all physicians know, may give fallacious evidence, and at times reaching a decision might be difficult

About a year ago one of my associates, Dr Thomas Horan, began the investigation of the kidneys of animals by making biopsies and later noting what effect the removal of the tissue might have on the parenchyma of the kidney He first injected trypan blue into the animal and then took a small section out of the kidney at various periods following the vital staining He was able to show that various stages of renal destruction could be demonstrated, he also was able to prove that such removal of tissue for biopsy had no serious effect on the function of the kidney

Following this, Dr Fred H Cole, of the Urology Department at Harper Hospital, and Dr Horan performed similar biopsy studies on a group of patients suffering from various types of nephritis and severe essential hypertension The specimen was removed with a specially devised instrument with which a small core, about 3 mm in diameter, could be safely taken from the kidney Histologic study of these specimens was most revealing

at the margin of the ribs, it was firm but otherwise normal. The gallbladder, the spleen and the kidneys were normal. There was no evidence of free fluid in the abdomen. The reflexes were normal. The temperature was 98.4 F. The weight was 110¼ pounds (50 Kg). Owing to the age of the patient and the absence of suggestive symptoms, a pelvic examination was deferred.

The chemical survey of the blood with respect to sugar, urea nitrogen, uric acid and chlorides gave negative results. The urine was normal. There was marked secondary anemia. Under the fluoroscope the heart was normal in size and position. There was prominence of the aortic knob, suggesting sclerosis. The right leaf of the diaphragm was judged to be adherent to the wall of the chest and moved little on inspiration. The left leaf was normal in contour and mobility. The pulmonary fields were relatively clear. The hilar shadows were exaggerated with considerable calcification. The electrocardiographic findings suggested a moderate degree of myocardial fibrosis. Roentgenographic study of the entire gastrointestinal tract showed no abnormality.

Three months later, in July, there was considerable edema of both feet. Clubbing of the fingers was noticed. There was persistent anemia of the secondary type. At this time the

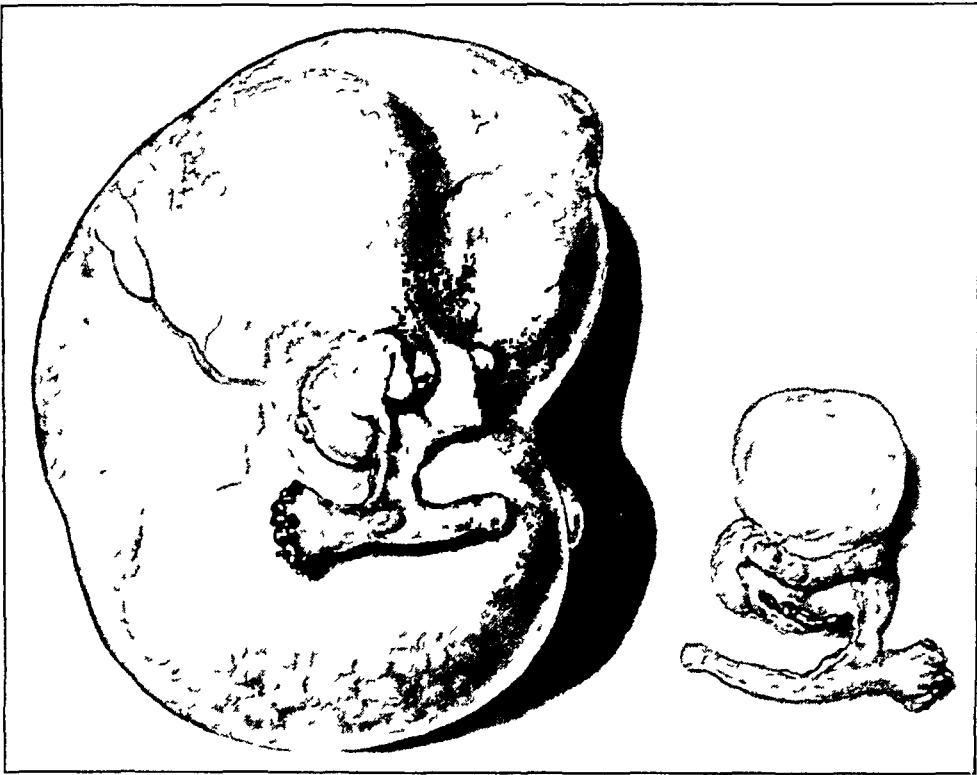


Fig 1—Bilateral fibroma with attached ovaries

signs of fluid at the base of the right lung were unequivocal. The first thoracentesis at our hands produced 1,000 cc of clear straw-colored fluid. The specific gravity was 1.021. A stained smear of the centrifugate showed a moderate number of red blood cells, 10 to 15 small mononuclears per high power field, and a few large mononuclears. No polymorphonuclear leukocytes were seen, nor cells containing mitoses. Cultures showed no growth. Guinea pig inoculations gave negative results. During the following fourteen months nine aspirations, each of at least 1,000 cc, were performed. Aspiration was done whenever dyspnea or thoracic discomfort and the physical signs of an appreciable amount of exudate demanded the procedure. Careful observation of the temperature during this time revealed no fever.

At first it was thought that we were dealing with a tuberculous process, perhaps a late flaring up of a latent process spreading from the calcified hilar lymph nodes. The absence of pain, of loss of weight and of other evidences of serious infection cast doubt on this preliminary impression.

Meanwhile a deferred pelvic examination revealed a tumor in the right side of the pelvis, about 3 inches (7.5 cm) in diameter, freely movable between the hands and strongly suggestive of an ovarian enlargement. At no time were there convincing signs of ascites. At



# ASSOCIATION OF HYDROTHORAX WITH OVARIAN FIBROMA (MEIGS'S SYNDROME)

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The mysterious association of fibroma of the ovary with hydrothorax has had infrequent notice in the literature of gynecology and none in that of internal medicine. The earliest recorded case seems to be that reported by Cullingworth<sup>1</sup> in 1879. In 1906 Griffith and Williamson<sup>2</sup> stated that "solid ovarian tumors are often accompanied by hydroperitoneum and sometimes by hydrothorax, this phenomenon has at present received no adequate explanation." In 1937 Meigs and Cass invited renewed attention to this syndrome. Again, in 1939, Meigs<sup>3</sup> emphasized its importance, collecting 15 cases from the literature, 6 from a single hospital. This suggests that the condition is less rare than has been believed. As such cases fall in that no man's land between the internist and the specialist, the significance of the combined thoracic, abdominal and pelvic features may be disregarded. The result of this is too often the denial of life-preserving surgical treatment because of an erroneous diagnosis of inoperable malignant tumor with widespread metastases.

The importance to the internist, as to the gynecologist, of keeping in mind the fact that a benign ovarian tumor may cause hydrothorax as well as ascites and that the simplest of laparotomies uniformly results in complete relief of the thoracic as well as of the abdominal features of the syndrome needs general recognition and emphasis.

## REPORT OF A CASE

This interesting, if limited, group was called to our attention by the case of a woman of 75 years, a widow with a history of five normal pregnancies. This patient had always been strong and well, without history of serious acute illness or of surgical operation. Her husband died one year before the first consultation, which was on April 30, 1940. Following her bereavement, the patient did not feel well, suffering from weakness, palpitation, depression and indifference to life. She had no pain and no symptoms referable to the digestive or genitourinary tracts. She noticed occasional edema of the ankles on effort but no loss in weight. She stated that one and a half years before fluid had been aspirated from the right thoracic cavity. She was a slight, pale woman, looking fully her age. The pupils were normal. The fundi revealed moderate arteriosclerotic changes. The mouth and the nares showed no evidence of a focus of infection. The thyroid gland was normal. There was no enlargement of the superficial lymph nodes. The heart was normal in size, position and sounds, without murmur. The rate was 88 and regular, the blood pressure was 140 systolic and 90 diastolic. The brachial vessels were thickened. The breasts were normal. Apart from emphysema and what was interpreted as pleural adhesions at the base of the right lung there were no signs of active disease in the chest. The edge of the liver was just felt

Presented before the Association of American Physicians, Atlantic City, N. J. May 6, 1942.

1 Cullingworth, C. J. Fibromas of Both Ovaries, *Tr. Obst. Soc. London* **21** 276, 1879.

2 Griffith, W. S. A., and Williamson, H. A System of Gynecology, London, Macmillan & Co., 1906, p. 442.

3 Meigs, J. V. Fibroma of Ovary, *Ann. Surg.* **110** 731-754, 1939. A complete bibliography may be found in this contribution.

color was ivory with occasional yellow to tan mottling. Numerous dilated veins coursed over the surface. The consistency throughout was firm. In the region of the hilus there was a harder, more lobulated area which was continuous with a small remaining part of what looked like normal ovarian tissue. The fallopian tube was normal in appearance. The left ovary was much smaller in size, measuring 3.5 by 4 by 3 cm. The hilus was very firm and nodular. Projecting from this was a smoother, rounded swelling, similar in appearance to the tumor of the right ovary except that it was more uniform in color and had not the large veins coursing on the surface.

**Microscopic Examination** The two tumors were similar in microscopic appearance. The surface was covered with a single layer of cuboidal epithelium which dipped down into deep clefts here and there. Immediately under this epithelial layer were interlacing bands of

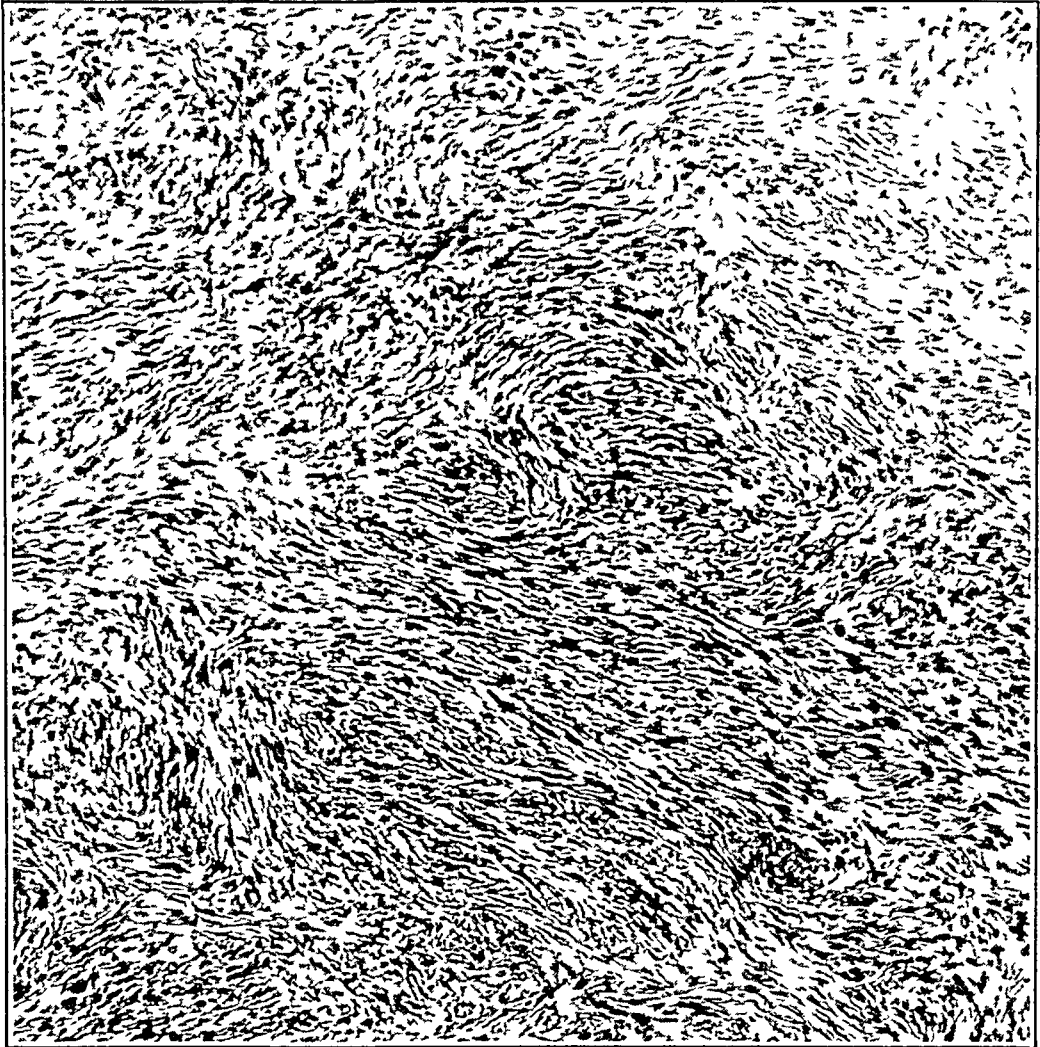


Fig 3—Microscopic section through the body of the tumor, showing typical fibroma

connective tissue which had the general appearance of ovarian stroma. In this were numerous corpora albicantia and corpora fibrosa. Beneath this layer was the tumor proper, which consisted of interlacing bands of fibrous tissue with connective tissue cells and fibrils. The cells were everywhere well formed and exhibited no tendency to rapid proliferation. Cross sections of the fallopian tubes showed the usual folds of mucous membrane covered with a single layer of tall columnar epithelium, which is a normal appearance in the fallopian tubes of a woman of this age.

**Pathologic Diagnosis** Bilateral fibroma of the ovary

**Subsequent Course**—Convalescence was uninterrupted. The last aspiration of the chest was done two days before the laparotomy, 1,100 cc of fluid being removed, with a small residue remaining. Postoperatively, the signs of remaining fluid cleared within a week.

this time, because of the obvious enlargement and firmness of the liver, with local discomfort, the possibility of cancer came to the fore. Rejecting this diagnosis because of the lack of progressive features, we were led to the consideration of Meigs's syndrome. Removal of the ovarian tumor was advised. Owing to the patient's advanced age and the hesitancy of the family, this was postponed for some months, during which the right side of the chest was aspirated repeatedly. Finally, on Feb 16, 1942, laparotomy was performed by one of us (B P W).

*Operation*—With the patient under anesthesia induced by intravenous instillation of a solution of pentothal sodium, the bladder was catheterized and the abdomen prepared and draped. Through a midline incision between the pubes and the umbilicus, the peritoneal



Fig 2—Microscopic section through the surface of the mass, showing ovarian tissue

cavity was opened, 200 to 300 cc of clear yellowish fluid was aspirated. The large tumor was found to involve the right ovary, which had a narrow pedicle. The left ovary was the seat of a smaller tumor and also had a narrow pedicle. Both pedicles were clamped and the ovaries removed. The pedicles were overstitched with fine catgut. The uterus contained several small subserous fibroid tumors which were not removed. Palpation of the liver revealed slight enlargement but no induration in the substance or on the surface. There were no other intraperitoneal pathologic findings. The abdominal wound was closed in the usual way and healed well. The patient had an afebrile convalescence and was discharged from the hospital two and a half weeks after healing of the wound.

*Pathologic Observations*—The specimen consisted of the right ovary and tube and the left ovary and tube.

*Macroscopic Examination*—The right ovary was round to ovoid and measured 13 by 9.5 by 9 cm. The surface for the most part was smooth with one or two indentations, the

patient was still anemic, the improvement in strength and her feeling of well-being were notable, suggesting the removal of some toxin-forming agent. Of interest and of possible importance was the postoperative change in the liver. This organ, previously large and firm, diminished in size and in hardness, returning to a seemingly normal status within six weeks. This is an item which merits further study in future cases.

#### ANALYSIS OF REPORTED CASES

In 1939 Meigs collected 15 cases from the literature since the first report of Cullingworth in 1879. The salient statistical points of these together with the case reported here may be given.

The extremes of age were 33 and 75. Our patient was by far the oldest on record. The average age was 51. Ten patients were married, 4 were single, the status of 2 was unrecorded. Seven of the patients had children, 5 were childless, no data in this respect were recorded for 4. In 3 patients the tumor was bilateral, in the rest, equally divided between the right and the left ovary. In 11 patients the effusion in the chest was on the right, in 3, on the left, in 1, bilateral, for 1 the side was not recorded. Three patients had no thoracentesis, 3 had but one, 3 had three, 1, four, 2, five, 1, seven, our own patient had 11, while for 2 there were "repeated" aspirations. Abdominal paracentesis was not required in 10 patients, 4 had but one, 1 was tapped four times, and 1 nine times. Ascites, therefore, seems less of a feature than hydrothorax.

At operation the amount of fluid in the peritoneal space varied from a small amount to 6 to 8 quarts (5.5 to 7.5 liters). In most cases it was less than 1,000 cc. The duration of symptoms was comparatively short in the average case. In all cases both the thoracic and the abdominal fluid vanished postoperatively. There was one death with necropsy. No pathologic changes in the pleura were described. The only abnormal finding in the chest was compression of the lung from long-standing and apparently neglected hydrothorax.

Thus far there has been no satisfactory explanation of the association of ovarian fibroma with hydrothorax and ascites. The possibility of an abnormal communication between the two serous cavities may be dismissed, since the amount of fluid in one cavity is not influenced by removal of fluid from the other. That a low level of serum protein is concerned seems unlikely. In the 2 cases in which the serum proteins were estimated no important variation from the normal was found. Again, if accumulations of fluid in the serous cavities were a result of diminution in serum proteins, edema of the subcutaneous tissues should be present. Although noted in our case, it was slight and transitory, while in most reported cases it was not observed.

Meigs mentioned the so-called "alarm reaction" of St. Karady, Brown and Selye. In rats these observers found that repeated, even minor traumas—physical or chemical—cause a resistance to be built up which lasts two or three months. With continuing action of the noxious agents, the animals lose their resistance and show decline in the output of urine, retention of water and at times collection of fluid in the pleural and peritoneal cavities shortly before death from toxæmia or shock. This being granted, it is difficult to understand why other ovarian tumors generally fail to give rise to hydrothorax.<sup>4</sup> For the present one must be content with the general statement that an ovarian fibroma in some manner wholly unknown

<sup>4</sup> Rarely other pelvic tumors give rise to hydrothorax. An example is found in the case of Salmon in which a large uterine fibroid with intraligamentous extension and follicular cysts of the ovaries was present with 300 cc of fluid in the peritoneum and 700 cc of bloody fluid in the chest. After removal of the tumor growths there was no recurrence of the hydrothorax.

There has been no recurrence of pleural fluid. Several subsequent fluoroscopic and roentgenographic studies of the chest, the last on April 29, 1942, disclosed no trace of pleural exudate. The costophrenic sinus on the right, the previously affected side, was altogether



Fig 4—Roentgenograms *A*, the chest before aspiration, showing right hydrothorax. *B*, the chest after aspiration, showing residue of fluid before laparotomy. *C*, the chest ten weeks after removal of the fibromas.

clear. The right leaf of the diaphragm descended normally on inspiration, as did the left. A slight increase in density of the lower lobe of the right lung may be interpreted as the result of repeated and long-continued compression from pleural exudate. Although the

# INCIDENCE AND CAUSES OF HYPERPROTEINEMIA

A STUDY OF 4,390 CASES

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We had observed 2 cases of relatively common diseases associated with hyperproteinemia (a case of subacute bacterial endocarditis and a case of cirrhosis and primary carcinoma of the liver)<sup>1</sup> The simultaneous presence of 2 patients with the supposedly rare condition of hyperproteinemia, lying side by side, in a small (200 bed) semiprivate hospital prompted a study of the incidence and the causes of this condition in our climate and locality This communication presents the results of a clinical-experimental investigation of this subject in a larger series of patients than has hitherto been reported

## LITERATURE

Jeghers and Selesnick,<sup>2</sup> summarizing the determinations of total plasma protein made by the clinical laboratories of the Boston City Hospital, reported that the incidence of total protein over 8 Gm per hundred cubic centimeters was 0.2 per cent of 557 determinations in 1934, 1.19 per cent of 526 determinations in 1935 and 2.4 per cent in 1936 These figures were compared with those for total protein less than 6 Gm per hundred cubic centimeters in the same series of cases, 69.5 per cent, 56.4 per cent and 49.2 per cent, respectively The increased incidence of high protein values in 1935 and 1936 reflected a greater number of blood protein determinations made specifically for hyperproteinemia in patients in whom multiple myeloma (a disease in which hyperproteinemia is common) was suspected This series represents determinations presumably made only when abnormal levels of blood protein were suspected and as such may not present a true general incidence Shuman and Jeghers<sup>3</sup> in a single medical service in the Boston City Hospital during April and May of 1939 found, in 320 successive determinations of blood

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\* Formerly Josiah Macy Jr Fellow in Medicine

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Chick embryo antigen (Lygranum) for the Frei test was furnished by E. R. Squibb & Sons  
Biological Laboratories

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1 Cardon, L., and others To be published

2 Jeghers, H., and Selesnick, S. Hyperproteinemia Its Significance, *Internat Clin* 3 248-279 (Sept) 1937

3 Shuman, H. H., and Jeghers, H. Value of Routine Blood-Protein Determinations *New England J Med* 222 335-339 (Feb 29) 1940

increases the permeability of the pleura. Whether reflexively, by the production of toxins that circulate with the blood, by allergic effects or by hormonal influence is altogether a matter of speculation.

#### SUMMARY

Sixteen cases are on record of the association of hydrothorax and ovarian fibroma. Such cases probably are more common than appears. Because they fall within two fields—internal medicine and gynecology—many are unrecognized or diagnosed erroneously as malignant tumor with metastases.

The cause of the association of ovarian fibroma and hydrothorax is quite unknown.

Removal of the fibroma results in complete and permanent cure of the hydrothorax.

Heretofore recognized, at least in medical writings, only by the gynecologist this syndrome should be considered by the internist in every case in which hydrothorax is encountered in a woman beyond the age of 30. This is especially needful if recurrent hydrothorax is not attended by fever, cachexia or loss of weight.

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As described by other workers, the increase in total protein concentration in our instances of "true" hyperproteinemia was found to be correlated with an increase in globulin concentration and usually with a concomitant decrease in albumin concentration

## COMMENT

Several major difficulties arise in the classification of our cases. We were first faced with the unsettled problem of eliminating hemoconcentration as the cause of increased concentration of serum proteins. Hemoconcentration<sup>7</sup> resulting from shock, venous stasis or dehydration has been given as one of the commonest causes of (apparent) hyperproteinemia. A study of the literature reveals that in many of the cases of hyperproteinemia reported these factors were not sufficiently taken into consideration. This fact may in part account for the wide variety of clinical conditions with hyperproteinemia hitherto reported. It is generally known that the state of hydration cannot be determined clinically with any degree of certainty. The usual clinical signs and symptoms may not become manifest until 6 per cent or more of the body weight in water has been lost. The exact amount of fluid that must be lost to produce apparent changes in the concentration of the blood is not yet known. According to the concept of Gamble,<sup>8</sup> the interstitial fluid, which is three times the volume of the plasma, serves as a reservoir to maintain the fluid and electrolyte balance of the circulating blood. Schiff<sup>9</sup> regarded the dehydration of the plasma and that of the interstitial tissues as running parallel, and Gregerson and Stewart<sup>10</sup> stated that work now in progress in their laboratories proves the volume of plasma is not independent of the quantity of interstitial fluid even with moderate changes in the total volume of extracellular fluid. We were interested in the state of hydration only as it affected the hydration of the blood. A patient may have a considerable increase in the total amount of available fluids with generalized edema, as in nephrosis, and yet manifest hemoconcentration.

The laboratory methods recently developed to determine the state of hydration are also fraught with misleading factors. Red blood cell and hematocrit determinations are of value only in the absence of anemia or polycythemia. Determinations of specific gravity and total serum protein must be discounted in the presence of pathologic conditions known to be associated with hypoproteinemia or hyperproteinemia. In chronic states of prolonged dehydration, the red blood cell count and the serum protein value tend to fall as a result of destruction of the red blood cells and serum proteins<sup>11</sup>. Since depletion of sodium is a significant factor in dehydration, it has been thought that the water loss can be computed from the sodium concentration in the blood plasma. However, Simeone and Sarris<sup>12</sup> stated that the total base of the blood plasma may remain normal in the presence of moderately severe dehydration if renal function is unimpaired. Nevertheless, low serum sodium may be definite evidence of dehydration. The determination of

7 Mandelbaum, H. Syndrome of Hemoconcentration, *Internat Clin* **2** 112-142 (June) 1936

8 Gamble, J. L., Extracellular Fluid, *Bull Johns Hopkins Hosp* **61** 151-173 (Sept) 1937

9 Schiff, E. Das Exiccoseproblem, *Ergebn d inn Med u Kinderh* **35** 519-603, 1929, *Klin Wchnschr* **8** 1105-1109 (June 11) 1929

10 Gregerson, M. I., and Stewart, J. D. Simultaneous Determination of Plasma Volume with T-1824 and "Available Fluid" Volume with Sodium Thiocyanate, *Am J Physiol* **125** 142-152 (Jan) 1939

11 Best, C. H., and Taylor, N. B. *The Physiological Bases of Medical Practice. A University of Toronto Text in Applied Physiology*, ed 2, Baltimore, Williams & Wilkins Company, 1939, p. 32

12 Simeone, F. A., and Sarris, S. P. Simple Method for Determination of Serum Protein. *J Lab & Clin Med* **26** 1046-1052 (March) 1941



proteins by the Kagan falling drop method, only 1 instance of hyperproteinemia (in a case of multiple myeloma) Bing<sup>4</sup> found 7 hyperglobulinemic serums (as determined by routine formaldehyde-gel tests ["formal"-gel tests]) among 3,697 serums examined. He concluded that in Denmark hyperglobulinemia is usually found only in patients with multiple myeloma or chronic infections. None of these series represents random sampling from all patients admitted to a hospital.

#### MATERIALS AND PROCEDURE

The recent introduction of the falling drop method has made possible routine, rapid and accurate determination of the total serum protein concentration on a large number of serums. To obtain patients with hyperproteinemia for detailed study, and to determine the incidence of this condition and the pathologic states associated with it, total protein was determined by the Kagan falling drop method<sup>5</sup> on 4,370 serums submitted to the department of serology of the Cook County Hospital for routine Kahn and Wassermann tests. This was done by the method of random sampling but did not include serum samples from the three divisions of the hospital—that for tuberculous patients, that for patients with contagious diseases and the pediatrics division. The number of patients admitted to these three departments constitute only 20 per cent of the total number admitted. More than half of the patients with tuberculosis are admitted first to the general hospital and consequently are included in this survey.

When a high level of total protein was discovered by the falling drop method, a fresh specimen was obtained from the patient for chemical determination of the concentrations of total protein, albumin and globulin and special tests as indicated in table 1. While we had no control over the technic of obtaining the original samples which were sent to the serologic laboratory, all subsequent samples of blood drawn by us were obtained with a minimum of venous stasis. It has been shown by Rowe<sup>6</sup> and others that the venous stasis produced by the application of a tourniquet for even a few minutes may result in an increase of serum proteins in the constricted extremity due to a transfer of water from blood to the tissues.

The frequency of lymphogranuloma venereum in the Cook County Hospital made it advisable to do the Frei test whenever possible. This test alone when positive may disclose the true cause of hyperproteinemia which might be otherwise attributed to another condition. In any case in which the Frei test was not performed, the absence of lymphogranuloma venereum could not be assumed with certainty.

#### RESULTS

Fifty-four cases in which the value for total serum protein was above 8.5 Gm. per hundred cubic centimeters were found in the examination of the serums of 4,370 patients by the falling drop method, giving an incidence of hyperproteinemia of 1.2 per cent. Of this series, obtained by random sampling, only 18 cases could be studied adequately. Seventeen additional cases in which hyperproteinemia had been noted were called to our attention by staff members of the hospital, and 3 cases were added from our private practice, making a total of 38 cases studied adequately. Our special interest in the relationship of hyperproteinemia to disease of the liver was known to our colleagues and explains the greater number of cases of hepatic disease referred to us.

In table 1 all of the pathologic conditions noted in each patient are given. Where one pathologic condition known to be a frequent cause of hyperproteinemia was found, we assumed that it was the main or only cause in that particular case. The conditions that were found to be associated with hyperproteinemia, listed in table 1, are summarized and classified in table 2.

4 Bing, J. Formolgel Reaction and Other Globulin Reactions, *Acta med Scandinav* **91** 336-356, 1937, *Hospitalstid* **80** 113-128 (Feb 2) 1937.

5 Kagan, B. M. Simple Method for the Estimation of Total Protein Content of Plasma and Serum. Falling Drop Method for the Determination of Specific Gravity, *J Clin Investigation* **17** 369-372 (July) 1938.

6 Rowe, A. H. Effect of Venous Stasis on the Proteins of Human Blood Serum, *J Lab & Clin Med* **1** 485-489, 1915.

39	N	granuloma venereum with rectal stricture and granululations, admitted to hospital in coma	3/19 3/21 4/ 1	25	3,150,000	60	10 13	2 17	7 66	0 32	1 plus		venereum, dehydration		
11 11	M W	Atrophic arthritis 9 yr., lymphogranuloma venereum 12 yr., with rectal involvement, stricture 8 yr., colostomy	1/16 1/21 5/13	None			11 41 9 50 8 71	1 37 3 85 2 95	7 07 5 65 5 79	0 62 0 63 0 51	1 plus	1 plus	Colostomy, blood transfusion, slight improvement	Lymphogranuloma venereum, atrophic arthritis	
12 27	F W	Lymphogranuloma with rectal stricture and colostomy, 1 yr	1/27 5/ 2 5/ 3	39	81	83 8 36 8 91	8 17	1 02	1 15	0 90	Neg	3 plus 2 plus	1 plus	Colostomy, discharged improved	Lymphogranuloma venereum
13 50	M W	Ulcers of glans penis with secondary malignant degeneration	12/19 12/31	1,200	None	9 87	9 50	3 09	6 41	0 48		1 plus	1 plus	Cystostomy, discharged	Lymphogranuloma venereum, carcinoma of penis
14 16	F N	Chronic stricture of rectum, admitted to hospital because of obstructive jaundice	1/31 2/ 4 2/18 1/30 6/19	1,800	None	63	8 98 9 38 7 99 9 90 9 22	3 27 3 16 3 16 3 31 5 07	5 71 6 22 4 83 6 59 4 15	0 57 0 51 0 66 0 50 1 22	1 plus	1 plus	Cholecystocholeoduodenostomy, biopsy of liver	Lymphogranuloma venereum, obstructive jaundice	
15 21	M N	Ulcers of penis with inguinal adenopathy (buboes)	11/21	None		9 15					1 plus	1 plus	1 plus	Discharged recovered	Lymphogranuloma venereum
16 19	F N	Moderate edema of hands and feet, frequency and burning on urination	3/21 3/25 1/ 9 4/10 4/21	1,500	None	59	8 53 10 15 6 61 7 16	3 65 3 61 3 16 2 16	1 88 6 51 3 18 5 30	0 75 0 55 0 91 0 11	4 plus 4 plus	4 plus	3 plus	Discharged improved	Chronic pyelonephritis, latent
17 55	M W	Epigastric pain, 30 lb (13 5 Kg) loss, frequency and burning on urination 3 mo duration	4/29 5/14 5/22 6/ 9 6/20	25	2,080,000	34	8 53	2 81	5 72	0 49	4 plus 4 plus 3 plus 2 plus	4 plus 4 plus 2 plus	1 plus	Nephrectomy, discharged recovered	Calculus, pyonephrosis
18 18	F In	Low grade fever, 15 lb (6 8 Kg) weight loss 1 mo., illian orange sized, tender, cystic mass in pelvis	6/16 6/20 6/24 6/26 7/25	19 17 22	3,040,000	45	9 38 10 01 12 76 10 10	3 65 3 50 4 68 3 15	5 73 6 51 8 08 6 65	0 61 0 51 0 58 0 52	4 plus 4 plus 4 plus	1 plus	Neg	Colostomy, purulent drainage, improved	Pelvic cellulitis (non specific)
19 76	M W	Diabetes 20 yr., infected gangrenous leg 8 wk., diabetic acidosis	1/28	2 plus	4,200,000	90	10 0	3 96	6 08	0 65		4 plus	Neg	Died, autopsy	Moist gangrene of leg with secondary infection, diabetes

\* The values shown were obtained by standard laboratory methods the sedimentation rate by the Westergren<sup>34</sup> method, the hematocrit by the Wintrobe<sup>35</sup> method (corrected by the method of Plasse and Bourke<sup>36</sup>), the Takata-Arn test according to the technic of A. B. Riggs (Value of the Takata and Arn Reaction as Diagnostic and Prognostic Aid in Cirrhosis of Liver, J. Lab. & Clin. Med. 20: 902-911 [June] 1935), the formaldehyde gel reaction according to the method of Klein, R. I., Levinson, S. A. and Skulik, C. K. Formal Gen Test During Rheumatic Fever of Childhood Comparison with Sedimentation Rate and Weimann Reaction, J. Pediatr. 18: 337-356 [March] 1941), the Frei test using chick embryo antigen, the total protein determinations by the Kagan<sup>37</sup> falling drop technic and the standard micro Kjeldahl method

† Ac means anticomplementary

TABLE 1.—Findings in Thirty-Eight Cases in Which Hyperlopiemema Was Present \*

Patient and Sex Age Color	History and Physical Findings	Date	Dehydration		Serum Protein										Diagnosis					
			Clini- cal	24 Hr Urine, Read- ing, Cc	Hema- to- crit %	Hemo- globin %	Red Cell Count	Total by Chemi- cally	Total Protein				Formal- dehyde			Sedimen- tation Rate, Mm		Klin Test	Wasser- mann Test	Course
									Tech- nic, per 100 Cc	Albumin, Gm 100 Cc	Globulin, Gm 100 Cc	A/G Ratio	Ar- senic Test	Al- dehyde Test		Orig- inal	Cor- rected			
1 17	Chronic alcoholism hemop- tysis, icterus, ascites, dependent edema	1/25 5/5 5/12	None	29	3,350,000	62	8.25 8.94 8.60	8.73 8.47	2.05 2.19	6.73 6.28	0.71 0.35	4 plus 4 plus	4 plus 4 plus	125 125	87 87	Neg	2 plus	Ac +	Discharged, with condition unchanged	Cirrhosis
2 18	Alcoholism (?), progressive painless jaundice	12/19 12/26 12/30	None		4,280,000	85	7.50 10.04 10.01	7.50 8.47	3.35 3.75	4.15 6.29 6.29	0.81 0.60 0.60						Neg	Discharged with condition unchanged	Cirrhosis	
3 27	Alcoholism, jaundice, en- largement of liver and spleen, ascites	1/22			1,950,000	47	9.38	2.87	6.51	0.44						1 plus	Neg	Died autopsy performed	Cirrhosis	
4 34	Alcoholism, chills, fever, jaundice, enlargement of liver	11/26 12/9	None		5,190,000	91	7.81	8.71 9.38 7.77	5.62 5.62	3.00 3.76	1.82 1.49						Neg	Complete recovery	Acute hepatitis	
5 59	Diabetes, jaundice, vomit- ing, diarrhea, enlargement of liver	3/29 1/7	None		4,380,000	72	8.73 8.53	3.15 3.75	5.18 4.78	0.65							Neg	Disch. un- improved	Cirrhosis	
6 31	Alcoholism, painless jaun- dice, enlargement of liver	2/3 2/10 2/24 4/1	None	2,200	1,450,000	87	8.99	6.71 9.18 6.62	3.7 4.94	3.01 4.44	1.23 1.11						Neg	Discharged improved	Cirrhosis	
7 17	Alcoholism, a condition which on several previous admissions was diagnosed as cirrhosis of liver, edema of ankles	4/17 4/21 4/21	None	36	4,360,000	82	7.84	9.33 8.35	5.51 6.12	4.17 2.23	1.25 2.71	1 plus	Neg				Neg	Discharged with condition unchanged	Cirrhosis	
8	Alcoholism, progressive enlargement of liver, severe cachexia, abdominal pain, diarrhea, enlarged nodular liver	3/8 3/13 3/15	None		1,800,000	62	13.30 8.06 9.50	3.33 2.79 3.75	9.77 5.27 5.75	0.76 0.53 0.65		2 plus	1 plus	105			Neg	Laboratory biopsy of liver, no autopsy	Cirrhosis of liver with primary carcinoma	
9 20	Painless jaundice, liver not palpable on 7/8 but enlarged on 7/10	7/8 7/16 7/19	None	34	1,000,000	68	7.80	8.71 8.53 7.33	5.02 4.91 5.10	1.36 1.38 2.12		1 plus	2 plus	100		Neg	Discharged improved	Catarrhal jaundice		
10	Long history of lympho	3/18	Marked				10.32	9.44	2.0	7.44	0.27	1 plus	4 plus	130	80	4 plus	Neg	Died on 1/7/11	Lympho- granuloma	



TABLE 1—Findings in Thirty-Eight Cases in Which Hyperproteinemia Was Present +—Continued

Pa- tient and Sex Age	History and Physical Findings	Date	Dehydration		Hema- to- crit	Hemo- glo- bin, %	Serum Protein										Sedimen- tation Rate, Mm			Wasser Kahn Test	Course	Diagnosis
							Olm cyl	24 Hr Urine, Cc	Read- ing	Red Cell Count	Tech Gm 100 Cc	Albu- min, Gm 100 Cc	Glob- ulin, Gm 100 Cc	A/G Ratio	Takata Ary Test	Formal- dehyde Gel Test						
			Total by Chem- ical	Total Deter- mined, Gm per 100 Cc	Albu- min, Gm per 100 Cc	Glob- ulin, Gm per 100 Cc											A/G Ratio	Takata Ary Test	Formal- dehyde Gel Test			
20 8	M Generalized erythema, pains W in joint, purulent dis- charge from ears, bloody urine, fever	11/10 11/18	None			2 800,000	54		9 38 10 04	4 94 5 26	4 14 1 78	1 11 1 10						Neg	Complete recovery	Scarlet fever, otitis media, arthritis, hemorrhagic nephritis		
21 11	M Generalized erythema, W strawberry tongue, desqua- mation, tender swollen joints	5/ 8 5/12	None		41	3,780,000	75		9 56 9 01	3 64	1 23	0 86				110	91		Neg	Complete recovery	Scarlet fever, acute arthritis	
22 38	F Prolonged fever, purulent W discharge from ear, erysipelas	5/ 6 5/ 9	None		30	3 500,000	67		8 87 7 35					Neg	Neg	100	52		Neg	Complete recovery	Erysipelas otitis media	
23 35	M Chills, fever, lumbar pain N urgency, frequency, burn- ing on urination, dryness of mucous membranes	4/16 4/18 4/22 4/23 4/25	4 plus 4 plus 2 plus None None		49	3,700,000	64		9 70 10 50 8 05 7 84 7 22							95	92		Neg Neg Neg	Intravenous injection of fluids, sulfonamide compounds, com- plete recovery	Acute pyelo- nephritis dehydration	
24 59	M 30 lb loss in 2 yr., cough, N dysphagia, fever, abdom- inal distention, emaciation, serum sodium low (128 mEq)	4/ 9 4/11 4/16	1 plus		50	4,000,000	62		10 1 8 87 9 01	2 34	6 15	0 18				85	85		Neg	Died, autopsy obtained	Bilateral pul- monary tuber- culosis, tuber- culous periton- itis, dehy- dration	
25 27	F Cough, loss of weight, night N sweats, acid fast bacteria in sputum, emaciation, roentgenogram of chest infiltration of left lung	3/26 3/30 4/ 7 4/28 5/12	None	1 600 900	20 34 31				8 73 9 11 9 15 9 60 9 38	2 90 3 16	5 52 5 0	0 15 0 63						Neg	Condition unchanged transferred to hospital for tuberculous patients	Pulmonary tuberculosis		
26 56	M Old history of rheumatic W heart disease, cough, fever, symptoms of congestive heart failure, petechiae, clubbing of fingers, enlarge- ment of liver and spleen	3/ 2 3/ 8 3/15 3/25 4/22	Mod- erate at times			3,200,000	50		10 90 8 12 12 10 8 06	1 70 1 84 1 33 1 11	6 20 1 38 7 77 3 95	0 76 0 90 0 56 1 04		Neg 1 plus Neg	Neg	110 129		Neg Neg	Ac Ac	Concomitant hyperthyroid- ism, improved after thyroid- ectomy	Endocarditis lenta (persis- tently nega- tive blood cultures)	
		10/25 11/11							8 78 7 84	4 69 3 86	1 09 3 98	1 15 0 97		Neg 1 plus	1 plus	125 59				Died autopsy	Hyperthy- roidism con- firmed by his tologic study	

may even drop to normal at times<sup>1</sup> Therefore, if a serum sample was obtained at a time when the protein concentration was temporarily normal, a case of hyperproteinemia might have been overlooked The number of cases thus overlooked was, no doubt, small

Still another difficulty was the frequency of cases in which multiple pathologic conditions occurred in the same patient As previously mentioned, when one pathologic condition known to be a frequent cause of hyperproteinemia was found we assumed that this was the main or only cause in that particular patient

In general, our findings confirm the observations of other workers

Hyperglobulinemia occurs in some types of hepatic disease, especially cirrhosis In the past it was commonly accepted that the change in the blood protein in cirrhosis consisted of diminution of the total protein concentration Recently various authors have demonstrated a rise in serum globulin in some cases of hepatic cirrhosis Published values as a rule revealed sufficient concomitant lowering of the serum albumin to maintain the total protein of a normal or even a lower than normal level, a situation not usually found in other diseases associated with hyperglobulinemia, in which hyperproteinemia usually resulted Thus Gutman and Wise<sup>14</sup> found globulin values of 6.0, 5.6 and 5.0 Gm per hundred cubic centimeters with corresponding total protein values of 8.4, 7.4, and 7.2 Gm in 3 cases of cirrhosis Peters and Eisenman,<sup>15</sup> in a series of cases, found the globulin above or in the upper range of normal in every case but 1 They stated "in cirrhosis of the liver globulin may rise far above the normal level" They cited other observers who had reported hyperglobulinemia in hepatic cirrhosis, and one who produced it by inducing experimental injury of the liver Foley, Keeton and others<sup>16</sup> stated "an increase in plasma globulin and a decrease in plasma albumin are associated not infrequently with chronic hepatic disease, particularly with cirrhosis of the liver"

Our series of 9 cases of hepatic disease includes 6 cases of hepatic cirrhosis, 1 of cirrhosis with a superimposed primary carcinoma of the liver, 1 of acute hepatitis in a patient with alcoholism in whom underlying cirrhosis or fatty liver could not be excluded, and 1 case of acute catarrhal jaundice in a young man It seems, then, that hyperglobulinemia (and hyperproteinemia) may also occur in some cases of acute hepatic disease In all of these cases the total protein was elevated, ranging between 8.0 and 13.4 Gm per hundred cubic centimeters We can give no reason for the occurrence of hyperproteinemia and hyperglobulinemia in some instances of certain types of hepatic disease and not in others

The common association of hyperproteinemia with lymphogranuloma venereum was demonstrated by the extensive pioneer studies of Gutman and his co-workers<sup>17</sup> In 26 of the 35 cases they studied the total protein values were above 8.0 Gm

14 Gutman, A. B., and Wise, C. R. Positive Formol-Gel Reactions Associated with Hyperglobulinemia in Lymphogranuloma Inguinale, Multiple Myeloma, and Hepatic Cirrhosis, *Proc Soc Exper Biol & Med* **35** 124-128 (Oct) 1936

15 Peters, J. P., and Eisenman, A. J. Serum Proteins in Diseases Not Primarily Affecting the Cardiovascular System or Kidneys, *Am J M Sc* **186** 808-833 (Dec) 1933

16 Foley, E. F., Keeton, R. W., Kendrick, A. B., and Darling, D. Alterations of Serum Protein as an Index of Hepatic Failure, *Arch Int Med* **60** 64-76 (July) 1937

17 Gutman, A. B., and Gutman, E. B. Calcium Protein Relation in Hyperproteinemia Total and Diffusible Calcium in Lymphogranuloma Inguinale and Myeloma, *Proc Soc Exper Biol & Med* **35** 511-515 (Dec) 1936 Gutman, A. B., Gutman, E. B., Jillson, R., and Williams, R. D. Acid-Base Equivalence of the Blood in Diseases Associated with Hyperglobulinemia with Special Reference to Lymphogranuloma Inguinale and Multiple Myeloma *J Clin Investigation* **15** 475-484 (Sept) 1936 Gutman and Wise<sup>14</sup>

blood volume by the dye methods and the computation of total available fluids by the thiocyanate or sucrose methods were too elaborate and time consuming for our work. The McClure-Aldrich intradermal wheal absorption test has not been proved to be a sufficiently sensitive index of the state of hydration. The opinion has been voiced that a patient is not dehydrated when the urinary output is adequate. This concept is not entirely correct, for it is known that in the presence of tubular damage the reabsorption of water is impaired and a large amount of dilute urine may be excreted even when the patient is dehydrated. Moreover, this type of renal damage, by its failure to conserve water and fixed base, may be a factor in the production of dehydration.

The picture is further complicated by the demonstration of Nadal and co-workers<sup>13</sup> that two distinct types of dehydration may occur in human subjects

TABLE 2—*Classification of Thirty-Eight Cases of Hyperproteinemia (Summary of Table 1)*

Condition	Number of Cases in Group	Cases of Each Type of Disease	Number of Each Case in Table 1
Hepatic disease	9		
Cirrhosis		6	1, 2, 3, 5, 6 and 7
Cirrhosis with primary carcinoma of liver		1	8
Acute hepatitis		1	4
Catarrhal jaundice		1	9
Lymphogranuloma venereum	6		10, 11, 12, 13, 14
Chronic suppurative infections	4		
Calculous pyelonephritis		1	16
Calculous pyonephrosis		1	17
Pelvic cellulitis		1	18
Moist gangrene of leg with diabetes mellitus		1	19
Acute infections	4		
Scarlet fever		2	20, 21
Erysipelas		1	22
Acute pyelonephritis		1	23
Tuberculosis	2		
Pulmonary, with tuberculous peritonitis		1	24
Pulmonary		1	25
Bacterial endocarditis	2		26, 27
Malaria	1		28
Syphilis (with hepatitis)	1		29
Multiple myeloma	1		30
Boeck's sarcoid	1		31
Extreme dehydration	2		
From vomiting and diarrhea		1	32
From diabetic coma		1	33
Miscellaneous conditions	6		
Generalized adenopathy (cause undiagnosed)		2	34, 35
Alcoholism with mental deterioration		1	36
Nonspecific ulcer of scrotum		1	37
Transverse myelitis (cause unknown)		1	38

They showed that dehydration resulting from simple deprivation of water is characterized by thirst and oliguria, and does not lead to impairment of circulation or to hemoconcentration, whereas dehydration resulting from abnormal loss of salt results mainly in loss of extracellular fluid, reduction of plasma volume, hemoconcentration and disturbances of the circulation.

Thus, it is apparent that objective determination of the state of hydration was impossible in most of our cases. Our interpretation of the state of hydration rested on clinical observations (vomiting, diarrhea, sweating, deprivation of water, thirst, dryness of mucous membranes, loss of turgor of tissue, oliguria) and on judicious evaluations, under the limitations mentioned, of the laboratory data listed under "Dehydration" in table 1.

Another difficulty that arose when we were interpreting our results was the fact that in hyperproteinemic states the blood protein levels may fluctuate daily and

13 Nadal, J. W., Pedersen, S., and Maddock, W. G. Comparison Between Dehydration from Salt Loss and from Water Deprivation, *J. Clin. Investigation* 20: 691-703 (Nov.) 1941.

tion is definitely increased while the total protein remains about normal" Lloyd and Paul<sup>23</sup> in 1928 wrote "it has of course been known for a long time that the globulins in syphilitic serum are increased" He studied 11 cases of secondary syphilis, all but 3 of which had values for globulin above 30 Gm per hundred cubic centimeters but only 1 of which had a total protein value above 80 Gm Wu<sup>24</sup> reported 2 cases of syphilis with hyperproteinemia Recently the occurrence of hyperglobulinemia and hyperproteinemia in uncomplicated syphilis has been questioned, and as demonstrated by Jones and Rome,<sup>15</sup> may be due to the concomitant presence of lymphogranuloma venereum The latter workers did not find marked increase in serum globulin in patients with syphilis except in those who also had a positive Frei test Unfortunately, the Frei test was not done in our single case of syphilis

The interpretation of the positive serologic reactions in 8 other cases in this table and the relation of hyperproteinemia to the false serologic reaction for syphilis and the anticomplementary Wassermann reaction constitute the subject of another report<sup>25</sup>

Salvesen<sup>26</sup> reported 3 cases of Boeck's sarcoid with hyperproteinemia One case of sarcoid is reported in this work

Only 1 instance of multiple myeloma occurred in our series This no doubt merely reflects the rarity of the condition, since hyperproteinemia and hyperglobulinemia occur with great frequency in cases of this disease Sweigert<sup>27</sup> cited 35 cases of multiple myeloma in which the blood proteins were determined, in 20 the values were over 80 Gm per hundred cubic centimeters Gutman and Gutman<sup>17</sup> in 1936 cited among 57 published cases of multiple myeloma 35 with hyperproteinemia Bing<sup>20</sup> added 14 cases of multiple myeloma with hyperglobulinemia These studies show that hyperproteinemia probably occurs in from 50 to 60 per cent of cases of multiple myeloma According to Jeghers and Selesnick it is of greater aid in the diagnosis of this condition than Bence Jones proteinuria The highest total protein values on record (up to 160 Gm per hundred cubic centimeters) have been reported with this disease

In the miscellaneous group in our series are 2 cases of undiagnosed generalized lymphadenopathy The clinical pictures in these patients were compatible with infectious mononucleosis in spite of negative heterophilic agglutination tests One case of transverse myelitis of unknown cause is reported Permission for an autopsy could not be obtained In this connection Bing and his collaborators reported 3 cases of a syndrome which apparently had never been published before "sepsis lenta with considerable involvement of the central nervous system and changes in the spinal fluid"

There were 2 cases in our series in which the hyperproteinemia was clearly due to dehydration alone One of the patients was a 56 year old Negro woman admitted to the hospital in diabetic coma The total protein on admission was 90 Gm per

23 Lloyd, R. B., and Paul, S. N. Protein Graphs in Kala-Azar, *Indian J. M. Research* **16** 529-535 (Oct.) 1928

24 Wu, H. New Colorimetric Method for Determination of Plasma Proteins *J. Biol. Chem.* **51** 33-39 (March) 1922

25 Cardon, L., and Atlas, O. H., with others. Biologic False Positive Reactions for Syphilis Associated with Hyperproteinemia. A Preliminary Report, *Arch. Dermat. & Syph.* **46** 713-720 (Nov.) 1942

26 Salvesen, H. A. Sarcoid of Boeck. Disease of Importance to Internal Medicine, *Acta med. Scandinav.* **86** 127-151, 1935

27 Sweigert, C. F. Multiple Myeloma with Hyperproteinemia, *Am. J. M. Sc.* **190** 245-256 (Aug.) 1935



per hundred cubic centimeters, 11.2 Gm being the highest value reached. The hyperproteinemia in their series was more marked in cases of rectal stricture. Jones and Rome<sup>18</sup> studied 79 patients with lymphogranuloma venereum, the majority of whom had total protein values above 8.0. The mean total protein value was 8.55, and the highest value obtained was 13.33 Gm per hundred cubic centimeters. Schamberg<sup>19</sup> studied the course of the plasma protein changes in 20 Negroes with early lymphogranuloma venereum treated with sulfanilamide. All of his patients presented initially hyperglobulinemia, the globulin reverting toward the normal level as clinical improvement was manifest. Seventeen of the 20 patients in his series had total protein values above 8.0 Gm at one time or another during the course of their disease. Jeghers and Selesnick<sup>2</sup> stated that since this disease is now known to be common in this country, it must always be considered when high blood protein is found, and excluded by the Frei test. Conversely, all persons with inguinal adenitis or rectal stricture should have blood protein determinations as part of their diagnostic study. The highest total protein value in our series of 6 cases of lymphogranuloma venereum was 11.44 Gm per hundred cubic centimeters and the highest globulin value 7.66 Gm.

Hyperglobulinemia and occasionally hyperproteinemia have been reported with various and usually chronic infections. Schamberg<sup>19</sup> stated that "hyperglobulinemia of greater or less extent occurs in most infectious diseases." Bing<sup>20</sup> stated that "the most frequent cause of hyperglobulinemia is an infection, and the increase of serum globulin has been placed in connection with the formation of antibodies, it having been shown that the function of antibodies is associated with the globulins." He stated further that "the hyperglobulinemia that occurs with the ordinary acute infections is only slight in most cases" and "in only rare cases is the increase of globulin so great that one can speak of hyperproteinemia as well." On the other hand, in chronic specific or nonspecific infections it is more often the case that hyperglobulinemia is so excessive that it leads to hyperproteinemia."

The cases of acute infection with hyperproteinemia in our series include 2 of scarlet fever, 1 of erysipelas and 1 of acute pyelonephritis.

The cases of chronic infection listed in our series include instance of various types of tuberculosis which have often been reported with hyperproteinemia and hyperglobulinemia. Kurten,<sup>21</sup> using the formaldehyde-gel test as an index of hyperglobulinemia, obtained a positive result in 60 to 80 per cent of cases of sub-acute bacterial endocarditis. Jeghers and Selesnick suggested that this disease will eventually be included in the group of diseases in which hyperproteinemia is common. Gutman included a case of this disease with high total protein and globulin values. Hyperproteinemia and hyperglobulinemia have been reported in cases of malaria. Chronic suppurative infections are conspicuous as a cause of hyperproteinemia in our series.

It was the opinion of earlier workers that syphilis produces an increase in globulin and total protein. Rowe<sup>22</sup> in 1916 stated that "in syphilis the globulin frac-

18 Jones, C. A., and Rome, H. P. Serum Proteins, Takata-Ara Reaction, and Liver Function Tests in Lymphogranuloma Venereum, *Am J Clin Path* **9** 421-436 (July) 1939.

19 Schamberg, J. L. Course of the Plasma Protein Changes in Early Lymphopathia Venereum Under Treatment with Sulfanilamide, *Am J M Sc* **201** 67-81 (Jan) 1941.

20 Bing, J. Further Investigations on Hyperglobulinemia (Occurrence and Degree of Hyperglobulinemia in Various Diseases. Ratio Between Hyperglobulinemia, Hyperproteinemia and Hypoalbuminemia, Formolgel-Reaction), *Acta med Scandinav* **103** 547-564, 1940.

21 Kurten, H. Zur Diagnose der Endocarditis lenta, *Ztschr f d ges exper Med* **61**-494, 1928.

22 Rowe, A. H. Albumin and Globulin Content of Human Blood Serum, *Arch Int Med* **18** 455-473 (Oct) 1916.

Kuiten's reaction) has been shown to be positive usually under the same conditions that produce a positive Takata-Ara reaction, and consequently it has been used as a simple method of detecting hyperproteinemia and hyperglobulinemia. The reaction depends on the formation of a gel when 36 per cent neutral solution of formaldehyde is added to blood serum. Bing<sup>20</sup> and others have shown that the reaction is positive whenever the globulin concentration is above 3.5 Gm per hundred cubic centimeters. Hassan and Salah<sup>30</sup> made a comparative study of the formaldehyde-gel and Takata-Ara reactions in relation to serum proteins. In 85 per cent of 600 serums examined there was similarity between the results of the two tests. They concluded that a strongly positive formaldehyde-gel reaction is always associated with hyperglobulinemia (usually euglobulinemia) and that such serums contain 4 per cent or more of globulin. The reaction cannot be applied as an absolute quantitative method for determining the degree of hyperglobulinemia but because of its simplicity and reliability can be used routinely to detect the presence of hyperglobulinemia.

Twenty-eight Takata-Ara tests and 30 formaldehyde-gel tests done in 20 of our cases of hyperproteinemia were positive regardless of the clinical condition causing the hyperproteinemia. In only 2 instances was there disagreement between the two tests. Of the 20 instances in which the values for the globulin fraction were available the lowest concentration of globulin to give a positive Takata-Ara or formaldehyde-gel test was 3.5 Gm per hundred cubic centimeters. These results also substantiate the observations of other workers that the formaldehyde-gel and Takata-Ara reactions are not specific for any particular diseases but are positive in any condition producing an increased concentration of globulin above 3.5 Gm per hundred cubic centimeters. The correlation of these two tests in conditions of hyperproteinemia shows that they are practically interchangeable, and since the formaldehyde-gel reaction is of greater simplicity, it may be conveniently substituted for the Takata-Ara reaction in detecting hyperglobulinemia.

(c) Increased Sedimentation Rate. The exact underlying mechanism of the increased rate of sedimentation of the red blood cells in various pathologic conditions is not as yet known although the literature on the subject is voluminous. Moreover, in spite of these extensive investigations, the present day knowledge of the exact cause of the increased rate is not much greater than the information contained in the pioneer work of Fahraeus<sup>31</sup>. He stated that although there was no correlation between the sedimentation rate and the concentration of total plasma protein, an increased concentration of globulin and of fibrinogen frequently occurred coincidentally with increased sinking velocity. He did not believe, however, that there was a direct relation of cause and effect. Ropes and his associates<sup>32</sup> concluded that there is not a quantitative correlation between the sedimentation rate and the concentration of fibrin, globulin or total protein. It has been frequently observed that hyperproteinemia is almost invariably associated with a markedly increased sedimentation rate even in the absence of fever or infection. In fact, some of the most rapid sedimentation rates on record have been associated with hyperproteinemia. Bendien and Snapper<sup>33</sup> stated that the following empiric

30 Hassan, A, and Salah, M. Comparative Study of Formol-Gel and Takata-Ara Reactions in Relation to Serum Proteins, *J Trop Med* **42** 169-174 (June 15) 1939.

31 Fahraeus, R. Suspension Stability of Blood, *Physiol Rev* **9** 241-274 (April) 1929.

32 Ropes, M. W., Rossmesl, E., and Bauer, W. Relationship Between Erythrocyte Sedimentation Rate and Plasma Proteins, *J Clin Investigation* **18** 791-798 (Nov.) 1939.

33 Bendien, W. M., and Snapper, I. Zusammenhang zwischen der Senkungsgeschwindigkeit der roten Blutkörperchen und dem Erweisspektrum, *Biochem Ztschr* **235** 14-34, 1931.

hundred cubic centimeters, of which 6.25 Gm was albumin and 2.75 Gm globulin (normal albumin-globulin ratio)

The other patient, a Negro man 50 years of age, gave a history of vomiting, diarrhea and little intake of food or fluid for a period of a week. The initial level of the total serum protein was 13.7 Gm per hundred cubic centimeters. Five days later, after the patient had been hydrated, the level of the total serum protein returned to 7.0 Gm per hundred cubic centimeters. Unfortunately, the levels of albumin and globulin were not determined.

Attempts to obtain other similar cases by examining the blood of patients that appeared clinically dehydrated were disappointing in that normal values for total protein were usually obtained even in several other cases of diabetic coma. The reasons for this may be twofold. First, the degree of dehydration necessary to produce hemoconcentration may be more extreme than is commonly thought, and, second, the usual indigent type of patient admitted to the Cook County Hospital frequently suffers from anemia and nutritional hypoproteinemia. However, in 8 of the 38 cases in this study, dehydration as manifested by clinical and laboratory signs was considered to contribute to the hyperproteinemia present.

*Special Tests*—(a) *Takata-Ara Reaction* The extensive and conflicting literature available concerning this recently popularized test was carefully reviewed and evaluated by Magath.<sup>28</sup> It has been generally thought that the test is positive in any case of disease associated with elevation of the serum globulin above 3 Gm per hundred cubic centimeters and a reversal of the albumin-globulin ratio. Magath, however, cited as many observers who denied this relationship as those who supported it. The conflicting results of various authors cited by Magath may be summarized as follows: (1) "in a high percentage of positive reactions the albumin-globulin ratio is reversed and in even a higher percentage there is some alteration in either the relative or the absolute amounts of these proteins" (2) "In an appreciable number of cases the albumin-globulin ratio is not disturbed when the Takata-Ara reaction is positive" (3) "Increase in the globulin fraction of the serum, both relatively and absolutely, does occur in the majority of cases, but there are many cases in which it does not. Conversely, there are many cases with changes in the globulin without positive Takata reactions" (4) "Many positive reactions are obtained in cases in which the level of serum protein is low and in which the albumin-globulin ratio is not reversed."

A study of the literature reveals that the Takata-Ara reaction is so frequently positive in cases of hyperproteinemia that it has been used as a simple means of detecting hyperproteinemia. Jegheis<sup>29</sup> noted markedly positive Takata-Ara reactions in each of 5 cases of multiple myeloma associated with hyperproteinemia and hyperglobulinemia. Jegheis and Selsnick reported the reaction positive in 9 of 10 cases of hyperproteinemia and hyperglobulinemia in which it was performed. Salvesen<sup>26</sup> reported the reaction positive in his cases of Boeck's sarcoid associated with hyperproteinemia, and it has been reported positive by numbers of workers in cases of lymphogranuloma venereum associated with increased protein concentration. Inasmuch as in hyperproteinemia it is globulin that is usually increased, it is understandable why a strongly positive reaction occurs in this condition.

(b) *Formaldehyde-Gel Reaction* The formaldehyde-gel reaction (known also as the formal-gel test, the Gate-Papacosta reaction, the Fox-Mackie reaction and

<sup>28</sup> Magath, T. B. Takata-Ara Test in Liver Disease, *J. Lab. & Clin. Med.* **26** 156-173 (Oct.) 1940.

<sup>29</sup> Jegheis, H. Detection of Hyperproteinemia Due to Multiple Myeloma by Means of Takata-Ara Reaction, *J. Lab. & Clin. Med.* **22** 425-430 (Jan.) 1937.

# BLOOD FLOW IN EXTREMITIES AFFECTED BY ANTERIOR POLIOMYELITIS

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It has generally been accepted that an extremity affected by anterior poliomyelitis, with atrophy of voluntary muscle, suffers from a definite diminution in blood supply. In fact, the rationale for some of the methods of treatment of this condition has had for a purpose the augmentation of the peripheral circulation through the involved muscles. Examination of literature, however, reveals that definite proof for such a view does not exist. In order to elucidate this point, the peripheral circulation in a series of 27 patients with anterior poliomyelitis was studied by means of the venous occlusion plethysmographic method.

## METHOD

The series was limited to subjects with unilateral involvement of an extremity, so that in each instance the contralateral normal limb could be utilized as a control. Readings of blood flow during rest, in cubic centimeters of blood per minute per hundred cubic centimeters of limb volume, were obtained either on two forearms or on two legs at a bath temperature of 32 C (temperature of the water in the plethysmograph) and a room temperature of 25 to 27 C, according to a technic previously described<sup>1</sup>. In the majority of subjects the response to a five minute period of local anoxia was also studied. This was measured by applying an arterial occlusion pressure to the extremity, proximal to its insertion in the plethysmograph, and then after release of the pressure determining blood flow every ten seconds during the subsequent state of reactive hyperemia<sup>2</sup>. From the readings obtained a graph was constructed, and by means of a planimeter the amount of excess blood flow, the quantity over and above that which would have ordinarily entered the extremity, was determined<sup>2</sup>. This figure was expressed as the quantity of excess blood per hundred cubic centimeters of limb volume elicited by each minute of arterial occlusion.

In most instances readings of cutaneous temperature were obtained repeatedly over a period of six hours by means of a Tycos dermatherm. During this time the subjects remained indoors.

## RESULTS

Of the 27 subjects in the series, 5 were tested within two to four weeks after the termination of the contagious stage of the disease. At this time atrophy of muscles was generally not significant, although definite weakness or paralysis of the extremities was present. In the remaining 22 subjects, the attack of polio-

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1 Abramson, D I, Zazeela, H, and Marrus, J. Plethysmographic Studies of Peripheral Blood Flow in Man. I. Criteria for Obtaining Accurate Plethysmographic Data, *Am Heart J* **17** 194 (Feb) 1939. Ferris, E B, Jr, and Abramson, D I. Description of a New Plethysmograph, *ibid* **19** 233 (Feb) 1940.

2 Abramson, D I, Katzenstein, K H, and Ferris, E B, Jr. Observations on Reactive Hyperemia in Various Portions of the Extremities, *Am Heart J* **22** 329 (Sept) 1941.

formula expresses the relation of the various factors involved in the sedimentation of the red cells

$$\text{Sedimentation rate} = \frac{45}{\text{cell volume}} \times [(\text{fibrinogen \%} - 3.5 \times 12 + (\text{globulin \%} - 22 \times 2.5)]$$

It can be seen from this formula that the sedimentation rate increases with the concentration of globulin but that other factors are also operative

Twenty-six sedimentation rates were determined by the Westergren<sup>34</sup> method in 17 cases of hyperproteinemia in our series, of which 23 were corrected for anemia by the hematocrit (Wintrobe and Buell<sup>35</sup>), according to the method of Plass and Rourke<sup>36</sup>. The mean of the 26 uncorrected sedimentation rates was 150 mm per hour (the normal does not exceed 20 mm per hour). Some of the values obtained were among the highest recorded in the literature and were seen even in the absence of fever or infection. The mean of the 23 corrected sedimentation rates was 80 mm per hour. The lowest corrected rate was 42. No linear correlation could be established between the concentration of total protein, albumin or globulin and the sedimentation rate, but one may conclude that in the presence of true hyperproteinemia the sedimentation rate is invariably increased to a marked degree.

Postmortem examination of 6 hyperproteinemic patients and biopsy of the livers of 2 hyperproteinemic patients failed to reveal any consistent histopathologic changes, such as the proliferation of the reticuloendothelial system suggested by Bing, except in the 2 cases of subacute bacterial endocarditis in which such proliferation was evident and in the case of multiple myeloma in which there was marked hyperplasia of plasma cells.

#### SUMMARY AND CONCLUSIONS

Fifty-four patients with total serum protein above 8.5 Gm per hundred cubic centimeters were found by random sampling examination of 4,370 serums, by the falling drop method giving the incidence of hyperproteinemia in the Cook County Hospital as 1.2 per cent.

In the Cook County Hospital hyperproteinemia is most frequently found to be associated with hepatic diseases, lymphogranuloma venereum, certain acute and chronic infections and states of extreme dehydration.

The concentration of total protein is correlated with the concentration of globulin in hyperproteinemic serums.

The results of the Takata-Ara and the formaldehyde-gel test are interchangeable and are almost invariably positive in conditions associated with hyperproteinemia and hyperglobulinemia.

The sedimentation rate is regularly increased to extreme degrees in hyperproteinemic conditions, but no linear correlation exists between the concentration of total protein or globulin and the rate of sedimentation.

No consistent correlation between particular histopathologic changes and hyperproteinemia could be demonstrated in this series of cases.

185 North Wabash Avenue  
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34 Westergren, A. Technique of Red Cell Sedimentation Reaction, *Am Rev Tuberc* 14 94-101 (July) 1926.

35 Wintrobe, M. M., and Buell, M. V. Hyperproteinemia Associated with Multiple Myeloma, with Report of Case in Which Extraordinary Hyperproteinemia Was Associated with Thrombosis of Retinal Veins and Symptoms Suggesting Raynaud's Disease, *Bull Johns Hopkins Hosp* 52 156-165 (Feb) 1933.

36 Plass, E. D., and Rourke, M. D. New Procedure for Determining Blood Sedimentation Rates, *J Clin Investigation* 5 531-539 (June) 1928.

less than, the same as or greater than those for the control side (table 1) In only 4 of the paralyzed extremities did the blood flow continue to be significantly decreased

In respect to the response to a period of arterial occlusion, examination of table 2 reveals that in 9 of 23 subjects the blood flow repayment was the same in the involved and in the normal extremity In 6 subjects it was slightly decreased, and in 3, slightly increased In only 5 was there any significant difference in the reaction of the blood vessels in the limb affected by poliomyelitis as compared with that on the control side, in 3 the response was greater than normal, and in 2 it was less than normal

In the case of determinations of cutaneous temperature the first set uniformly showed a significant decrease on the paralyzed side, in some instances to the extent

TABLE 2—*Response to a Five Minute Period of Arterial Occlusion in an Extremity Affected by Poliomyelitis as Compared with That in the Contralateral Normal Side*

Subject No	Normal Limb			Involved Limb			Comment
	Resting Flow *	Repayment †	Maximum Single Reading ‡	Resting Flow *	Repayment †	Maximum Single Reading ‡	
			1 forearm				
1	22	21	130	53	33	114	Acute stage past
3	31	10	91	44	34	176	Chronic
5	32	28	189	29	26	63	Chronic
4	33	25	152	40	22	106	Chronic
6	41	31	181	18	12	97	Chronic
			1 leg				
8	49	36	211	52	14	135	Acute stage past
7	21	24	121	20	25	194	Acute stage past
26	14	07	59	07	04	56	Chronic
16	19	07	70	25	06	67	Chronic
14	12	20	148	49	26	177	Chronic
11	52	14	113	51	14	101	Chronic
13	33	30	154	46	24	155	Chronic
18	28	09	92	19	19	104	Chronic
12	52	16	139	64	09	112	Chronic
17	18	18	78	16	13	101	Chronic
22	30	19	165	20	16	92	Chronic
20	20	16	55	14	12	69	Chronic
10	41	14	109	51	18	134	Chronic
23	34	25	156	52	25	122	Chronic
27	67	11	135	46	11	91	Chronic
19	27	17	69	28	19	150	Chronic
24	40	10	87	12	14	62	Chronic
25	40	16	93	23	16	157	Chronic

\* The blood flow was read in cubic centimeters per minute per hundred cubic centimeters of limb volume

† Repayment was calculated as the amount of excess blood per hundred cubic centimeters of limb volume entering an extremity in a period of reactive hyperemia for each minute of arterial occlusion

‡ The maximum single reading represented the highest rate of blood flow obtained during a period of reactive hyperemia

of 5 C (table 3) However, with the second and the third set, taken three and six hours, respectively, after the first one, the difference between the normal and the abnormal limb definitely diminished with the result that in many subjects the readings for both limbs were the same by the time the six hour experimental period was terminated (table 3)

#### COMMENT

When determinations of blood flow are made on a series of normal subjects with the venous occlusion plethysmographic method, it is assumed that the relative amounts of skin, muscle, fat and bone in the limb are fairly constant in every instance Since the blood flow through bone is not measured with this procedure it is generally accepted that the reading, although expressed as the number of cubic centimeters of blood per minute per hundred cubic centimeters of total limb volume, actually represents the composite rate of circulation through skin and muscle

myelitis had taken place from one to thirty years previously and marked involvement of muscle existed in most instances. There was no apparent difference in the rates of blood flow observed in the two groups (table 1), and hence the results will be discussed collectively.

TABLE 1—*Blood Flow During Rest in an Extremity Affected by Anterior Poliomyelitis as Compared with That in the Contralateral Normal Limb\**

Blood Flow, Cc / Min /100 Cc of Limb Volume				Blood Flow Cc / Min /100 Cc of Limb Volume			
Subject No	Normal Limb	Abnormal Limb	Comment	Subject No	Normal Limb	Abnormal Limb	Comment
Forearm							
1	25 22	55 52	Acute stage past	4	50 11 2	25 37 51	Chronic definite atrophy
2	14	30	Acute stage past	5	32 29 5	26 26 28	Chronic definite atrophy
3	30 32	50 38	Chronic definite atrophy	6	37 42 39	13 17 15	Chronic definite atrophy
Leg							
7	21 21	20 22	Acute stage past	18	20 26 30	16 22 29	Chronic definite atrophy
8	55 15	5 10	Acute stage past	19	24 24 29	11 11 51	Chronic definite atrophy
9	45 9	67 11	Acute stage past	20	17 17	15 13	Chronic little atrophy
10	41 40 11	46 47 55	Chronic definite atrophy	21	12	08	Chronic some atrophy
11	51 53	38 65	Chronic definite atrophy	22	29 31 30	14 24 24	Chronic definite atrophy
12	51 55	62 74 63	Chronic definite atrophy	23	56 32 15	27 5 29	Chronic definite atrophy
13	36 1	36 37 55	Chronic definite atrophy	24	27 6 12	09 15 21	Chronic definite atrophy
14	59 38 46	48 50	Chronic definite atrophy	25	10 58 36	20 24 22	Chronic definite atrophy
15	17	24	Chronic, definite atrophy	26	15 14	07 08	Chronic definite atrophy
16	23 20 12	19 24 19	Chronic, definite atrophy	27	70 50 69 65	22 42 52 62	Chronic definite atrophy
17	19 16 20	12 16 18	Chronic definite atrophy				

\* Each reading represents the average of ten determinations. In most of the subjects at least three sets of readings were made during the experimental period, at half hour intervals. These are presented in the table in the order they were obtained.

When the readings obtained at the beginning of the experimental period were examined, it was found that in 14 instances the average blood flow in the involved extremity was either the same as or definitely greater than that in the control contralateral limb (table 1). The readings for the affected limb in the remaining 13 subjects were either somewhat or definitely reduced. However, on making further determinations over the next hour or two, an increase in the rate of blood flow in the paralyzed extremities was observed in the latter subjects. In fact in 9 of them the second set of readings now yielded values which were either only slightly

in the quantity of muscle mass. In other words, the bone and to a lesser degree, the skin now contributed a relatively greater than normal share of the total volume of the atrophied extremity. In view of the fact that the blood flow through bone is not measured by the plethysmographic method, it would seem that measurements of blood flow obtained in an atrophied extremity should be corrected for this factor. If it were possible to do this, it would tend to increase, and certainly not decrease, the magnitude of the readings of blood flow obtained in this type of a limb. In the light of this, our readings for extremities affected by poliomyelitis assume definite significance since with the exception of a few instances there was no difference observed between the rate of blood flow in the involved extremity, as compared with that in the control limb. Correction of these readings of blood flow would certainly not detract from the validity of this observation.

The occurrence of an initial low cutaneous temperature supports the clinical impression that an extremity affected by poliomyelitis is colder to touch than the contralateral normal limb, these data imply that the cutaneous circulation is reduced in this condition. In accord with this are the reports of a number of investigators<sup>3</sup> who have found that an excessive amount of spasm exists in the peripheral vessels in anterior poliomyelitis. In fact, sympathectomy has been advocated for the relief of this symptom.<sup>4</sup> The rise in cutaneous temperature that took place over a period of six hours, however, does not completely support such a point of view. The first set of readings of cutaneous temperature was obtained only a short time after the subjects had come in from the outside (all the tests having been performed during the winter months), while the subsequent determinations were made after the skin had been exposed to the environment of a warm room for three to six hours. The rise in cutaneous temperature of the paralyzed extremity can probably be attributed to this circumstance, thus implying that there is no continuous spasm of the cutaneous blood vessels in the affected limb, but only that these vessels respond more markedly to the stimulus of cold than do those of the normal side. Under physiologic conditions, with an optimal environmental temperature, there is no difference in the cutaneous circulation of the two extremities, provided sufficient time has elapsed for the disappearance of the vasoconstriction produced in the cutaneous vessels of the paralyzed limb by cold.

These changes in cutaneous temperature can help to explain the low initial readings of blood flow obtained in the affected extremity in some of our subjects. Since, as previously stated, a composite flow through both skin and muscle is obtained with the plethysmographic method, at the beginning of the experimental period the readings probably represented the portion contributed by the muscle alone, the cutaneous circulation being minimal because of the existing vasospasm. Later, as this was removed and the flow through skin reached a normal level, the total blood flow likewise rose, until it was equal in magnitude to that of the control extremity.

The finding that the circulatory response to a period of arterial occlusion was approximately the same in both the atrophied and the normal extremity appears to have definite significance in relation to the metabolism of the various tissues in the limb. The rationale for such a procedure is based on the assumption that during the period that an artery is occluded by pressure the tissues affected are incurring a blood flow debt, since metabolic processes still continue. On removal of the

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3 (a) Telford, E. D., and Stopford, J. S. B. Some Experiences of Sympathectomy in Anterior Poliomyelitis, *Brit. M. J.* **2**: 770 (Oct.) 1933. (b) Harris, R. I., and MacDonald, J. L. The Effect of Lumbar Sympathectomy upon the Growth of Legs Paralyzed by Anterior Poliomyelitis, *J. Bone & Joint Surg.* **18**: 35 (Jan.) 1936.



only In the case of an atrophied extremity, the question arises whether the normal proportion of skin, muscle and bone is disturbed and, further, if it is, whether a figure indicating the rate of blood flow per hundred cubic centimeters of limb volume in this type of limb can be compared with a similar reading for a normal limb

TABLE 3—Changes in Cutaneous Temperature in an Extremity Affected by Anterior Poliomyelitis and in the Contralateral Normal Extremity

Subject No	Upper Extremity				
	Arm, Lower Third	Forearm			Hand, Dorsum
		Upper Third	Middle Third	Lower Third	
2	-0.5 -0.3 +0.5	-0.1 -0.1 -0.1	-0.5 -0.4 -0.5	-1.0 -0.5 ±0.0	-0.7 -0.7 +0.2
6	-2.0 -1.5 -1.3	-1 -0.9 -1.3	-1.2 -0.9 -1.5	-1.6 -0.6 -1.2	-0.3 -0.1 -0.5
5	-1.6 -0.7 -0.1	-0.6 -0.1 -0.5	-0.7 -1.2 ±0.0	-0.1 -0.1 -0.3	-1.1 -0.1 ±0.0
4	-1.3 -1.0 +0.3	-0.7 -0.6 -0.7	-0.6 -0.5 -0.3	-0.6 -0.1 -0.3	-0.1 -0.1 -0.1
Subject No	Lower Extremity				
	Thigh, Lower Third	Leg			Foot Dorsum
		Upper Third	Middle Third	Lower Third	
23	-0.8 -0.6 -0.3	-1.6 -1.0 -0.5	-4.2 -3.9 -1.9	-3.9 -4.1 -1.7	-1.2 -4.0 -2.2
27	-0.5 -0.5 -0.2	-0.5 -0.4 -0.6	-2.1 -1.7 -2.3	-1.5 -1.2 -2	-1.1 -0.6 -2.5
12	-1.2 ±0.0 -0.5	-1.1 -0.1 -0.4	-0.5 -0.1 -0.2	-2.9 -2.9 -0.2	-1.0 -1.8 ±0.0
13	-1.8 -0.4 +0.2	-1.8 -1.1 -0.7	-2.2 -1.4 -0.7	-1.9 -1.1 -0.1	-2.1 -1.2 -0.2
22	+0.2 -0.6	-2.4 -1.9	-2.9 -0.9	-2.9 -0.5	-2 -1.4
20	+0.3 -0.3 -0.5	-0.1 -0.2 +0.1	-0.8 -1.2 -0.1	-1.7 -1.4 -0.4	-0.7 -0.7 -0.7
18	-1.4 -1.3 -0.9	-2.6 -2.0 -0.6	-2.6 -2.6 -2.6	-2.3 -1.6 -2.4	-3.7 -0.9 -3.3
17	-0.9 -0.4	-1.4 -1.9	-2.5 -2.6	-3.6 -2.6	-3.8 -4.2
19	-0.2 -0.1 -0.1	-2.0 -0.1 -1.2	-2.9 -0.7 -0.3	-2.1 -0.4 +0.1	+0.1 -1.0 -0.1
21	-2.4 -0.9 -0.1	-3.1 -0.4 -0.1	-3.3 -1.4 -1.1	-2.9 -1.0 -0.6	-1.1 -0.9 ±0.0
10	-2.2 -0.6	-3.2 -1.2	-3.9 -3.0	-5 -2.8	-5.4 -3.7
14	-1.6 -0.5 -0.3	-1.0 ±0.0 -0.1	-1.3 -1.4 -0.2	-1.1 -0.8 -0.3	-2.4 -0.6 -0.1

\* The readings are set down in the order obtained i.e. at the beginning in the middle and at the end of the six hour experimental period. Each figure represents the difference between the cutaneous temperature of the normal extremity and that of the abnormal extremity, the minus sign indicating that the temperature is greater on the normal side and the plus sign indicating that it is greater on the involved side.

In order to elucidate this problem in respect to poliomyelitis roentgenograms were taken of the normal and the paralyzed limbs of a number of subjects on the same plate and with a single exposure. In all instances it was found that although a definite decrease in the volume of all the tissues existed, the greatest loss occurred

# SERUM CHOLESTEROL LEVEL IN CORONARY ARTERIOSCLEROSIS

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Previous studies<sup>1</sup> have demonstrated an apparent constancy of the serum cholesterol level in normal persons during long periods of observation. It is therefore considered of interest to determine whether or not the serum cholesterol level in patients with coronary arteriosclerosis behaves in a similar manner.

The literature on this subject is not conclusive, and it is based on single determinations of the blood cholesterol in varying numbers of subjects, arbitrarily designated as arteriosclerotic persons and normal controls. From a study of 13 patients with arteriosclerosis and 9 normal persons, Bachmeister and Henes,<sup>2</sup> in 1913, concluded that patients with arteriosclerosis in the stage of development showed an increase in blood cholesterol. In the same year Weltmann<sup>3</sup> reported that 11 of 12 persons with arteriosclerosis had increased blood cholesterol. Denis,<sup>4</sup> in 1917, found that 5 of 14 patients with arteriosclerosis had values for blood cholesterol that exceeded those of 20 control persons. Gorham and Meyers<sup>5</sup> reported in that year that the range of cholesterol levels in 10 patients with arteriosclerosis exceeded that in 14 normal persons. In a well controlled experiment, Mjassnikow<sup>6</sup> stated that 16 patients, 14 of whom suffered from angina pectoris, had elevations in serum cholesterol, the values ranging from 190 to 440 mg per hundred cubic centimeters. Twenty-five control persons' serum cholesterol amounted to from 120 to 170 mg per hundred cubic centimeters.

Stepp<sup>7</sup> and Andes, Kampmeier and Adams<sup>8</sup> failed to substantiate the foregoing results. The latter investigators in determining whether or not arteriosclerosis was present in a group of Negroes used as criteria the condition of the radial and dorsalis pedis arteries. (Stiffness of these arteries is now considered evidence

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1 Turner, K. B., and Steiner, A. A Long Term Study of the Variations of Serum Cholesterol in Man, *J Clin Investigation* **18** 45, 1939. Steiner, A., and Turner, K. B. Observations on the Serum Cholesterol in Acute Infections as Recorded During and After Pneumonia, *ibid* **19** 373, 1940. Steiner, A., and Domanski, B. Dietary Hypercholesterolemia, *Am J M Sc* **201** 820, 1941.

2 Bachmeister and Henes. Untersuchungen über den Cholesteringehalt des menschlichen Blutes bei verschiedenen inneren Krankheiten, *Deutsche med Wchnschr* **34** 544, 1913.

3 Weltmann, O. Zur klinische Bedeutung des Cholesterinnachweises im Blutserum, *Wien klin Wchnschr* **26** 874, 1913.

4 Denis, W. Cholesterol in Human Blood under Pathological Conditions, *J Biol Chem* **24** 93, 1917.

5 Gorham, F. D., and Meyers, V. C. Remarks on the Cholesterol Content of Human Blood, *Arch Int Med* **20** 599 (Oct) 1917.

6 Mjassnikow, A. L. Klinische Beobachtungen über Cholesterinämie bei Arteriosklerose, *Deutsches Arch f klin Med* **143** 403, 1924.

7 Stepp, W. Ueber den Cholesteringehalt des Blutserums bei Krankheiten, *München med Wchnschr* **65** 781, 1918.

8 Andes, J. E., Kampmeier, R. H., and Adams, C. C. Studies on Plasma Protein and Cholesterol in Normal White and Colored Individuals, and in Negroes with Arteriosclerosis, *J Lab & Clin Med* **21** 340, 1936.

pressure, a period of reactive hyperemia ensues, during which state the blood flow debt is repaid through an increased quantity of blood entering the extremity per unit of time. Hence, the magnitude of this repayment would be a reflection of the requirements of the tissues regarding blood flow. Our data, therefore, are in accord with the view that the metabolism of muscles atrophied by poliomyelitis is no different from that of normal muscles.

#### SUMMARY AND CONCLUSION

The rate of blood flow during rest was measured by the venous occlusion plethysmographic method in a series of 27 subjects with acute or chronic anterior poliomyelitis of one extremity.

It was found that in the majority of cases the peripheral circulation in the paralyzed limb was the same as that in the contralateral normal extremity, in fact, in some instances it was even significantly greater.

Evidence was obtained which indicated that the cutaneous blood vessels in the extremity affected by anterior poliomyelitis respond more markedly to the stimulus of cold than do those of the contralateral normal limb. The response takes the form of excessive vasoconstriction on exposure to a low environmental temperature and is apparent as a significant decrease in cutaneous temperature.

By studying the changes in blood flow during the reactive hyperemia elicited by a period of arterial occlusion, some evidence was obtained which suggested that the metabolism of muscles atrophied by poliomyelitis is the same as that of normal tissues.

In view of the lack of evidence for the hypothesis that in persons with anterior poliomyelitis the peripheral circulation is reduced, it is concluded that those treatments which have for an aim the increase in blood flow through the affected parts should be critically reexamined for their therapeutic value.

Miss M. Meador, principal, and Mrs. D. Wartman, Miss E. G. Fiefield and Miss R. Pratt, of the Department of Physiotherapy of the Randall J. Condon School, cooperated in this study.

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the lowest serum cholesterol had values ranging from 236 to 409 mg per hundred cubic centimeters, while the one with the highest had values varying between 455 and 550 mg per hundred cubic centimeters

The average serum cholesterol values for the individual patients varied from 296 to 499 mg per hundred cubic centimeters and the mean of the averages for the group was 355 mg per hundred cubic centimeters. The standard deviations for the individual patients varied from 15.8 to 38.8, the average standard deviation for the group being 24.8

TABLE 1—*Variation of the Serum Cholesterol Level in Fifteen Patients with Coronary Arteriosclerosis*

Patient	Age	Sex	Months of Observation	Cholesterol Determinations	Value, Mg per 100 Cc		
					Range	Average *	Standard Deviation
1 M C	64	F	22	41	333-462	389 ± 73	27.5
2 T D†	46	M	26	74	236-409	319 ± 90	36.2
3 L I†	43	M	25	60	337-410	377 ± 42	20.0
4 Y H	61	F	20	50	265-360	308 ± 52	24.4
5 N O	47	M	20	30	292-417	343 ± 63	38.8
6 F K†#	42	M	8	25	250-329	296 ± 46	19.4
7 A G	48	M	15	52	264-357	312 ± 48	21.9
8 T J†	66	M	12	25	269-331	299 ± 32	15.8
9 J M	61	M	6	29	248-333	285 ± 48	22.3
10 E O	52	M	12	71	286-411	352 ± 66	31.1
11 L R†#	47	M	2	8	417-508	471 ± 55	28.3
12 H G#	55	M	8	52	352-446	401 ± 49	19.0
13 E R#	72	F	9	30	290-373	318 ± 55	25.4
14 R B†#	47	F	6	13	325-469	360 ± 49	22.4
15 L E#	72	M	6	12	455-550	499 ± 51	19.5
				Total 572			
				Av 38	Mean 355		Av 24.8

\* The average is given with the maximum deviation from the mean

† Dextrose tolerance was normal

# The values for serum proteins were normal

TABLE 2—*Variation of the Serum Cholesterol Level in a Control Group of Fifteen Persons*

Patient	Age	Sex	Months of Observation	Cholesterol Determinations	Value, Mg per 100 Cc		
					Range	Average *	Standard Deviation
1 D C	22	M	18	30	220-249	234 ± 15	6.9
2 B S	35	M	9	20	265-285	273 ± 12	4.7
3 T R	72	M	18	37	216-238	222 ± 10	5.7
4 A P	73	F	18	32	315-355	334 ± 19	11.6
5 J N	54	M	18	33	286-336	308 ± 28	17.5
6 H T	42	F	20	38	211-301	278 ± 23	14.5
7 F K	64	M	24	40	230-280	256 ± 26	13.8
8 C P	28	F	10	9	218-235	224 ± 11	6.3
9 I O	47	M	24	42	244-296	268 ± 24	13.7
10 D C	15	F	13	10	200-238	214 ± 24	10.3
11 J S	34	M	4	8	228-248	240 ± 12	7.1
12 L J	38	F	5	21	273-294	283 ± 10	6.7
13 A N	52	M	3	7	227-239	231 ± 8	3.2
14 C R	50	M	4	8	220-236	226 ± 10	4.6
15 M G	35	M	4	7	225-236	232 ± 7	4.3
				Total 342			
				Av 22.6	Mean 255		Av 8.7

\* The average is given with the maximum deviation from the mean

These results may be compared with those in table 2, which shows the data for the control group. The average period of observation for the control group was twelve and six-tenths months, and the average number of cholesterol determinations for each person was 22.6, a total of 342 serum cholesterol determinations. The range of serum cholesterol levels in the control persons varied from 216 to 238 mg per hundred cubic centimeters to 315 to 355 mg per hundred cubic centimeters. The average serum cholesterol of the subjects lay between 214 and 334 mg

favoring a diagnosis of medial sclerosis [Monckeberg's] ) Page, Kirk and Van Slyke<sup>9</sup> and Elliot and Nuzum,<sup>10</sup> in studies designed to determine whether or not the serum cholesterol in patients with essential hypertension was elevated, stated that the presence or absence of arteriosclerosis did not seem to influence the cholesterol level. However, in the first of these papers the criteria for the presence of arteriosclerosis were not elaborated on. In the second paper the statement was made that in 18 of 53 patients with hypertension arteriosclerosis of moderate to marked degree as measured by palpation of the peripheral arteries and by ophthalmic examination was present. The blood cholesterol level was not significantly elevated.

The most comprehensive study of this problem is that of Davis, Stern and Lesnich,<sup>11</sup> published in 1937. These authors in a study of the blood lipids and cholesterol in 59 patients with angina pectoris and in 54 controls, found that there was considerable overlapping of the serum cholesterol values in the two groups, but that a small number (20 per cent) with angina pectoris showed values well above the highest normal value.

The present paper records consecutive observations on the serum cholesterol in 15 patients with coronary arteriosclerosis and in 15 relatively normal persons similar with regard to age, all of whom were closely followed over periods up to two years.

#### METHODS

The group of patients with coronary arteriosclerosis consisted of 15 persons, 13 of whom had electrocardiographic evidence of proved coronary occlusion, whereas the remaining 2 had angina pectoris. The latter 2 patients had positive anoxemia tests<sup>12</sup> for coronary insufficiency. The patients with coronary occlusion were not included in this series until six weeks after the time of the coronary occlusion. Moderate hypertension was present in 2 of these patients.

The control subjects consisted of 7 patients who had recovered six months previously from pneumococcal pneumonia and who had no apparent disease at the time of this study. The remaining 8 persons in the control group had various diseases which were in a stationary (inactive) phase. These were peptic ulcer, tabes dorsalis, rheumatic heart disease, thrombosis of the inferior vena cava and controlled diabetes mellitus. The serum cholesterol of each person was determined by the method of Bloor, Pelkan and Allen<sup>13</sup> twice weekly, then weekly and finally at bimonthly intervals during the period of observation. The basal metabolism of each subject was determined by the Benedict-Roth method. The urine was examined for glycosuria and the blood sugar during fasting was determined, for each person, at frequent intervals.

#### RESULTS

Table 1 shows the range of values for serum cholesterol in each patient with coronary arteriosclerosis. The number of months of observation, the number of cholesterol determinations, the average cholesterol value with the maximum deviation, and the standard deviation for each of the patients also are tabulated. The periods of observation for the patients with coronary arteriosclerosis varied from two to twenty-six months, and averaged thirteen months for the group. The number of serum cholesterol determinations totaled 742, and the number per patient varied from 8 to 74, averaging 38 for the group. The patient with

9 Page, I. H., Kirk, E., and Van Slyke, D. D. Plasma Lipids in Essential Hypertension, *J. Clin. Investigation* **15** 109, 1936.

10 Elliot, A. H., and Nuzum, F. R. Cholesterol Content of Whole Blood in Patients with Arterial Hypertension, *Arch. Int. Med.* **57** 63 (Jan.) 1936.

11 Davis, D., Stern, B., and Lesnich, G. The Lipid and Cholesterol Content of the Blood of Patients with Angina Pectoris and Arteriosclerosis, *Ann. Int. Med.* **11** 354, 1937.

12 Levy, R. L., Barach, A. L., and Bruenn, H. G. Effects of Induced Oxygen Want in Patients with Cardiac Pain, *Am. Heart J.* **15** 187, 1938.

13 Bloor, W. R., Pelkan, K. F., and Allen, D. M. Determination of Fatty Acids (and Cholesterol) in Small Amounts of Blood Plasma, *J. Biol. Chem.* **52** 191, 1922.

Although statistically the aforementioned results are significant, it was felt desirable to make observations on a larger number of patients. For this reason a single determination of serum cholesterol was made on each of 15 additional consecutive patients, aged 40 through 66 years, who were found to have had coronary thrombosis in the absence of diabetes mellitus. Single determinations of serum cholesterol were made on 30 additional normal persons aged 28 through

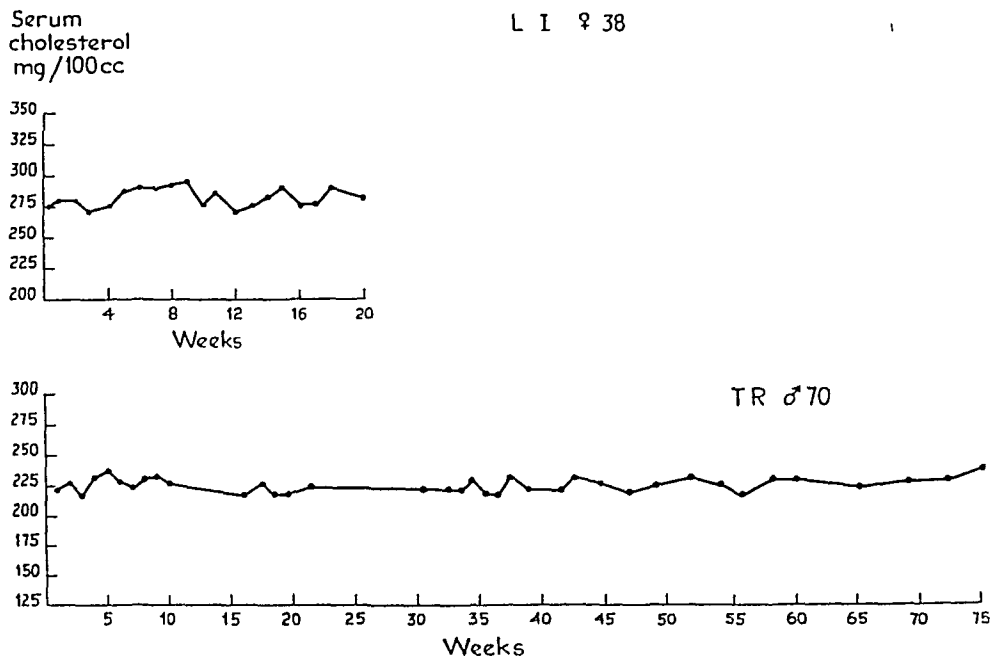


Chart 2—Variation in serum cholesterol level in 2 controls

TABLE 3—Comparison of the Serum Cholesterol Levels in Fifteen Additional Patients with Coronary Arteriosclerosis and in Thirty Normal Subjects

Serum Cholesterol, Mg per 100 Cc, in Patients with Coronary Arteriosclerosis		Serum Cholesterol, Mg per 100 Cc, in Normal Subjects		
1	284	1	176	239
2	279	2	178	248
3	294	3	185	250
4	297	4	185	250
5	305	5	193	252
6	312	6	203	252
7	315	7	212	252
8	315	8	213	259
9	335	9	215	263
10	335	10	216	264
11	342	11	216	270
12	355	12	216	278
13	369	13	217	292
14	380	14	218	314
15	505	15	220	337
Average 336		Average 236		

65 years. In the second group of patients with coronary thrombosis the serum cholesterol values varied from 264 to 505 mg and averaged 336 mg per hundred cubic centimeters (table 3). The range of serum cholesterol in the normal persons varied from 176 to 337 mg per hundred cubic centimeters and averaged 236 mg. The results confirm the previous observations.

COMMENT

The data presented indicate that the serum cholesterol level in patients with coronary arteriosclerosis is significantly higher than that in a group of control

per hundred cubic centimeters. The mean of the average serum cholesterol determinations for the control group was 255 mg per hundred cubic centimeters. The standard deviation for the control patients varied from 3.2 to 17.5, and the average standard deviation for the group was 8.7.

From these two tables it can be seen that serum cholesterol was generally higher in the patients with coronary arteriosclerosis than in the control group. Charts 1 and 2 graphically demonstrate the differences between the serum cholesterol values of the two groups. Statistical analysis of these results shows a significant difference between the values of serum cholesterol for the patients with arteriosclerosis and the values for the control group (tables 1 and 2). According to this analysis, there is less than 1 chance in 1,000 that the numerical differences between the two groups could have been obtained by chance.

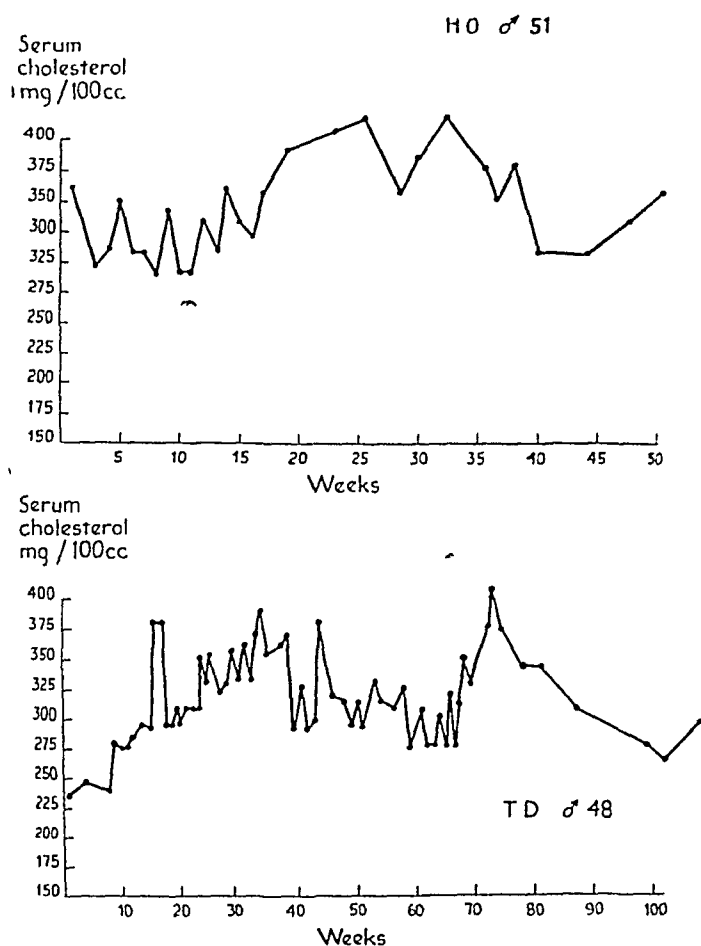


Chart 1—Variation in serum cholesterol level in 2 patients with coronary arteriosclerosis

From tables 1 and 2 it is also seen that the fluctuation of the serum cholesterol level of patients with coronary arteriosclerosis is greater than that of the control group. The standard deviation, which is a measure of this fluctuation from the mean, varied from 15.8 to 38.8 in the group with coronary arteriosclerosis and from 3.2 to 17.5 in the control series. The average standard deviation for the former group was 24.8, in contrast to 8.7 for the control group. The ratio of the standard deviation of the group with coronary arteriosclerosis to that of the control group is thus  $24.8/8.7 = 2.8$ . It may be shown that the probability of this ratio occurring by chance is only 0.02 (1 chance in 50). Charts 1 and 2 illustrate this excessive fluctuation in 2 patients with coronary arteriosclerosis in contrast with the relatively constant values in 2 persons of the control group.

# MULTIPLE BILATERAL PULMONARY ADENOMATOSIS IN MAN

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A pulmonary lesion of sheep, apparently of infectious origin but resembling a tumor in its morphologic characteristics, has been known since about 1891<sup>1</sup>. It has received such varying names as jagziekte, epizootic adenomatosis, pulmonary adenomatosis and infectious adenomatosis. Very similar and probably identical conditions have been reported under the titles of verminous pneumonia and Montana progressive pneumonia of sheep. A considerable incidence has been found in areas as widely separated as South Africa, Saxony, England, Iceland and Montana. Similar changes have been seen in horses<sup>3</sup> and guinea pigs,<sup>4</sup> and as early as 1903 Lohlein<sup>5</sup> found a picture resembling it in a 69 year old woman. Since that time, the veterinary literature on the subject has become voluminous and there have been several other human cases recorded.

## REPORT OF A CASE

A white man aged 42 was admitted to the Wisconsin General Hospital April 19, 1941, with a cough of two years' duration. The cough had been dry originally, but for a year he had raised about 1 cupful of frothy watery sputum daily. There was never any hemoptysis, but some pain in the upper anterior part of the chest was associated with the cough. For some months he had noticed gradually increasing weakness, a profuse nasal discharge, frequent cold sweats, a low grade fever in the afternoon, shortness of breath on even such slight exertion as talking, decreasing appetite, belching, "gas pains" and progressive loss of weight amounting to 40 pounds (18 Kg) by the time of admission.

He was a railroad machinist, and he had had no known contact with sheep, nor had he traveled extensively in sheep-raising areas so far as his family knew. Past illnesses included only the usual children's diseases and a rather vague rheumatic episode which had involved a number of joints, with transient local pain and swelling, during the spring of 1940, almost a year after the onset of his present illness. There had been no known infection of the respiratory tract preceding the present illness except for very occasional acute coryza. The family history included no pulmonary diseases so far as he knew, nor had there been known contact with any otherwise.

He was a pale, emaciated (height, 65 inches [165 cm], weight, 88 pounds [40 Kg]), febrile, sick-appearing person, who seemed quite weak and coughed frequently, raising copious amounts of clear watery whitish sputum. The fingers and toes were markedly clubbed, and there was moderate cyanosis of the nails and the mucosae. There was a mucopurulent nasal discharge with some mucosal swelling and injection. The cardiac findings were normal except for tachycardia (rate 100 to 130). The blood pressure was 100 systolic and 70 diastolic.

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1 Eber, A. Bericht uber das Veterinarwesen im Konigreich Sachsen fur das Jahr 1891, p. 43, cited by Pallaske.<sup>2</sup>

2 Pallaske, G. Zur Kenntnis der sogenannten Adenomatose oder der multiplen Adenome d'un corynebaccille diphteroïde, Bull. Assoc. franç. p. l'étude du cancer **15** 212-237, 1926.

3 Theiler, A. Jaagsiekte in Horses, in Seventh and Eighth Reports of the Director of Veterinary Research, Union of South Africa, April 1918, p. 59.

4 Grumbach, A. Tumeurs epithéliales du poumon chez le cobaye a la suite d'injection d'un corynebaccille diphteroïde, Bull. Assoc. franç. p. l'étude du cancer **15** 212-237, 1926.

5 Lohlein, M. Cystisch-papillare Lungentumor, Verhandl. d. deutsch. path. Gesellsch. **12** 111-115, 1908.



subjects and also that the cholesterol level in the former group fluctuates widely in contrast with the relative constancy of the level in the control group. Since other disease states may be associated with an elevated level of serum cholesterol (such as uncontrolled diabetes mellitus, chronic glomerulonephritis, nephrosis and myxedema), certain tests were made in order to rule out the possible presence of these conditions. Sugar tolerance tests on 6 patients (table 1) indicated absence of diabetes. Likewise in 6 patients serum proteins showed no abnormalities (table 1). The basal metabolic rates of the 15 patients also fell within normal limits. In view of these findings it is unlikely that the aforementioned diseases were present.

The significance of the present findings cannot be fully evaluated at this time. However, it may be pointed out that the association of elevation and fluctuation of the serum cholesterol level has been considered by many observers to be of etiologic significance in the frequent, premature and widespread development of arteriosclerosis in patients with uncontrolled diabetes mellitus, myxedema, chronic glomerulonephritis and xanthomatosis.

Marked variation and graduation in the extent and the age of cholesterol deposits (atheromas) in arteries is a frequent observation. The process of deposition appears to be discontinuous. It is possible that these variations in the deposits of cholesterol are related to corresponding periods of abnormal fluctuation and elevation of the serum cholesterol level. Coronary arteriosclerosis can now be added to the list of conditions frequently associated with increased serum cholesterol. The mechanism responsible for these changes in serum cholesterol in patients with coronary arteriosclerosis is not apparent.

#### SUMMARY

The serum cholesterol levels of 15 patients with coronary arteriosclerosis and of 15 controls were determined at frequent intervals for periods up to two years.

The average serum cholesterol values for individual patients with coronary arteriosclerosis varied from 308 to 499 mg per hundred cubic centimeters with a mean average of 355 mg. The average serum cholesterol values for the controls varied from 214 to 334 mg per hundred cubic centimeters, with a mean average of 255 mg. This difference between the two groups was found to be statistically significant.

The fluctuation of the serum cholesterol level in the group with coronary arteriosclerosis as measured by the standard deviation varied from 15.8 to 38.8 and averaged 24.8. The fluctuation of the serum cholesterol level of the control group varied from 3.2 to 17.5, with an average of 8.7. The ratio of 2.8 between the average standard deviations was found to have statistical significance.

Single determinations of serum cholesterol in 15 additional patients with coronary arteriosclerosis and in 30 additional controls present data confirmatory of the long term study.

#### CONCLUSIONS

1 The serum cholesterol level in patients with coronary arteriosclerosis is significantly higher than the serum cholesterol level in normal subjects.

2 The serum cholesterol level in patients with coronary arteriosclerosis is inconstant and fluctuates widely.

3 The claim of relative constancy of the serum cholesterol level in normal persons is further substantiated.

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sclerosis and some slight residual myocardial changes from an earlier rheumatic fever. The only other significant changes were in the lungs and their associated lymph nodes.

Each pleural cavity contained about 100 cc of serosanguineous fluid, and on the surface of the lower lobe of the right lung there were a few small granular fibrin deposits of recent origin. About the upper lobe of this lung and in the interlobar fissures of both lungs were a few fine fibrous adhesions. The lungs themselves seemed rather voluminous and did not collapse when removed.

The surface of the right lung was smooth, except as already noted, and pinkish gray with anthracotic mottling. The lung was quite heavy and felt firm, it was subcrepitant and full of irregular nodules beneath the pleura. Its cut surface was in most areas pinkish yellow, smooth and meaty in appearance, with fine strands of gray-white tissue separating great numbers of closely packed round or polygonal nodules a few millimeters to several

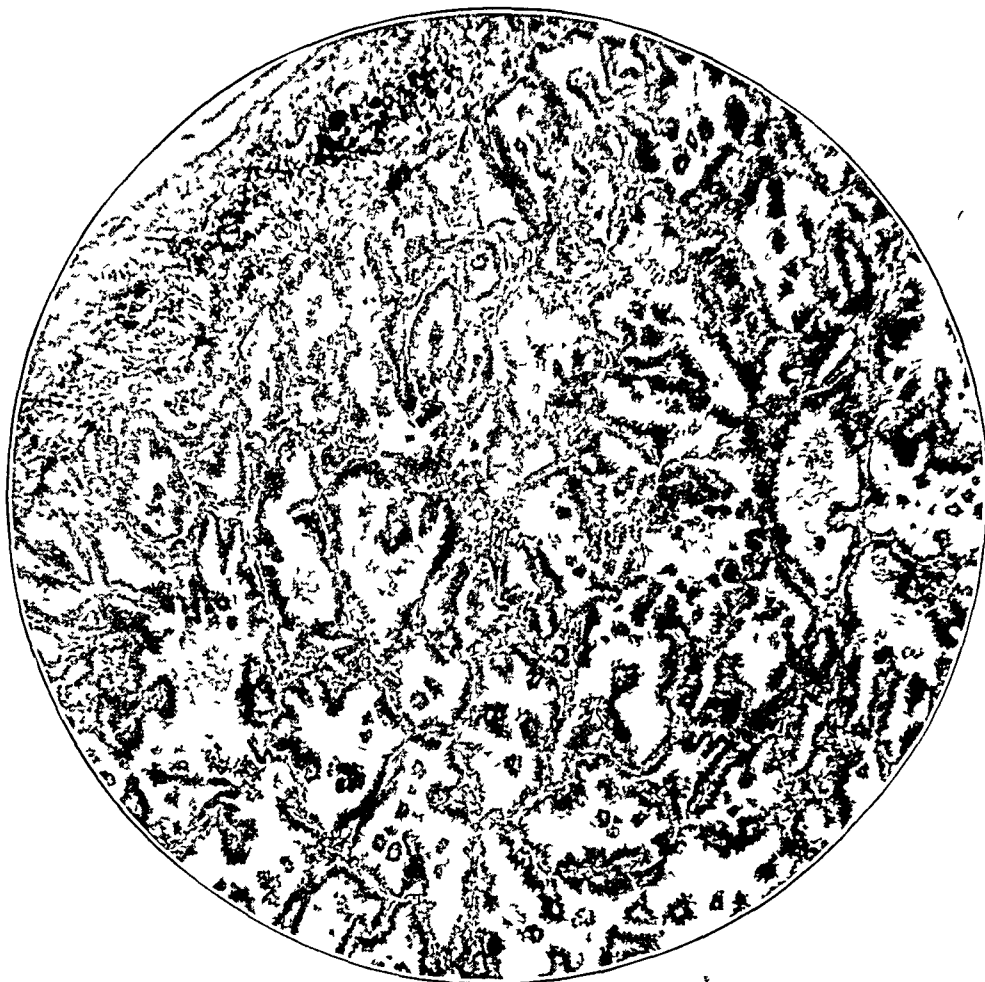


FIG 2—Section from a subpleural nodule. The pleura is thickened but not invaded by the epithelial change. The normal alveolar framework is preserved and covered by a single layer of tall columnar cells, sometimes thrown up into papillary folds. The alveolar exudate is evident. Hematoxylin and eosin stain,  $\times 10$  objective and ocular.

centimeters in diameter. Here and there were small patches of what appeared to be congested and edematous but still crepitant and somewhat emphysematous lung tissue.

The left lung showed similar but much less extensive nodularity beneath a perfectly smooth pleura and was generally subcrepitant to crepitant except for purplish meaty consolidated areas posteriorly. The cut surface was moist, exuding quantities of pinkish frothy fluid, and showed numerous patchy areas resembling the bulk of the right lung. The intervening areas showed purplish meaty consolidation posteriorly and edema with alternating patchy atelectasis and emphysema anteriorly.

The trachea and the bronchi were filled with a frothy brownish fluid, and their mucosae were somewhat injected, but nowhere, as far as they could be followed, could any tumor growth be detected in them. The major vessels seemed normal except for slight atheromatous changes. The hilar and tracheobronchial nodes were slightly enlarged, moderately

The right hemithorax was smaller than the left, with bilaterally limited expansion and inspiratory retraction of the interspaces. The respirations were 20 to 40 per minute, shallow and labored. Impaired resonance and increased tactile fremitus were noted over the entire right side of the chest, especially posteriorly, and at the left base, with tubular breathing on the right over the posterior surface and a small area of the midlung field anteriorly. Numerous moist rales were audible over the entire chest. The spleen was not palpable, and there was no significant lymphadenopathy. The remainder of the physical findings seemed within the limits of normal.

The hemoglobin content was 15.4 Gm, and the white cell count 16,500, with 93 per cent neutrophils, 4 per cent lymphocytes and 3 per cent monocytes. The neutrophils all showed toxic changes, and there were many stab forms. The values for blood sugar and nonprotein nitrogen were normal, the results of routine urinalysis were not remarkable and the Wassermann test of the blood was negative. Two sputum specimens examined did not show acid-fast bacilli.

A stereoscopic roentgenogram of the chest obtained April 20 was reported on as follows by Dr. L. W. Paul: "The heart is about in midposition. The right border is not well seen, but I doubt that it is enlarged. There is some soft patchy mottling throughout the left



Fig. 1—Cut surface of the right lung. The absence of color contrast makes reproduction of detail unsatisfactory, but the extensive nodular involvement replacing almost the entire parenchyma except for the two dark areas in the upper lobe is visible. The pleura where seen is smooth and not involved by the adenomatous process.

middle and lower lung fields, although no large areas of consolidation are present here. The left dome of the diaphragm is smooth, and the sulcus is clear. On the right there is a great deal of soft opacity, almost completely obscuring the aerated lung except for some air in the apex and peripherally at the base. The peripheral part of the dome of the diaphragm is visible, with a clear sulcus. Medially the dome is obscured by pulmonary changes."

The course of illness in the hospital was that of an acute fulminating pneumonic process, with progressive dyspnea and cyanosis and increasingly numerous coarse moist rales obscuring other pulmonary auscultatory findings. There was a spiking temperature with a daily variation of 3 to 4 degrees and with peaks of 105 to 106 F, and the respiratory rate rose to about 50 per minute. The white blood cell count fell to a total of 3,700, with 88 per cent neutrophils, 10 per cent lymphocytes and 2 per cent monocytes. The patient became increasingly lethargic and confused, and died April 24, 1941.

Autopsy was performed four hours after death. Clubbing of fingers and toes, cyanosis and emaciation were again noted. The abdominal panniculus measured only 1 to 2 mm in its thickest portion. There were early generalized arteriosclerosis and arteriolar nephro-

In no area could any involvement of the pleura, the bronchi, the blood vessels or the lymphoid structures be detected, in spite of careful and extensive study. The tracheobronchial tree showed only catarrhal inflammation, with an occasional respiratory bronchiole showing epithelial changes adjacent to an alveolar opening, and no larger divisions being affected anywhere. The pleura showed a slight general fibrous thickening but was nowhere invaded by epithelial growth. The hilar and bronchial lymph nodes showed small lymphoid follicles spread apart by sinuses distended with fluid containing strands of fibrin and large numbers of neutrophils and mononuclear phagocytes, but not the slightest evidence of neoplastic involvement.

Cultures of blood from the heart gave no bacterial growth, and only staphylococci were recovered from the pulmonary tissues. Careful microscopic study revealed no fungi, protozoa or wormlike parasites, and stains for acid-fast bacilli and Gram stains of lung tissue showed

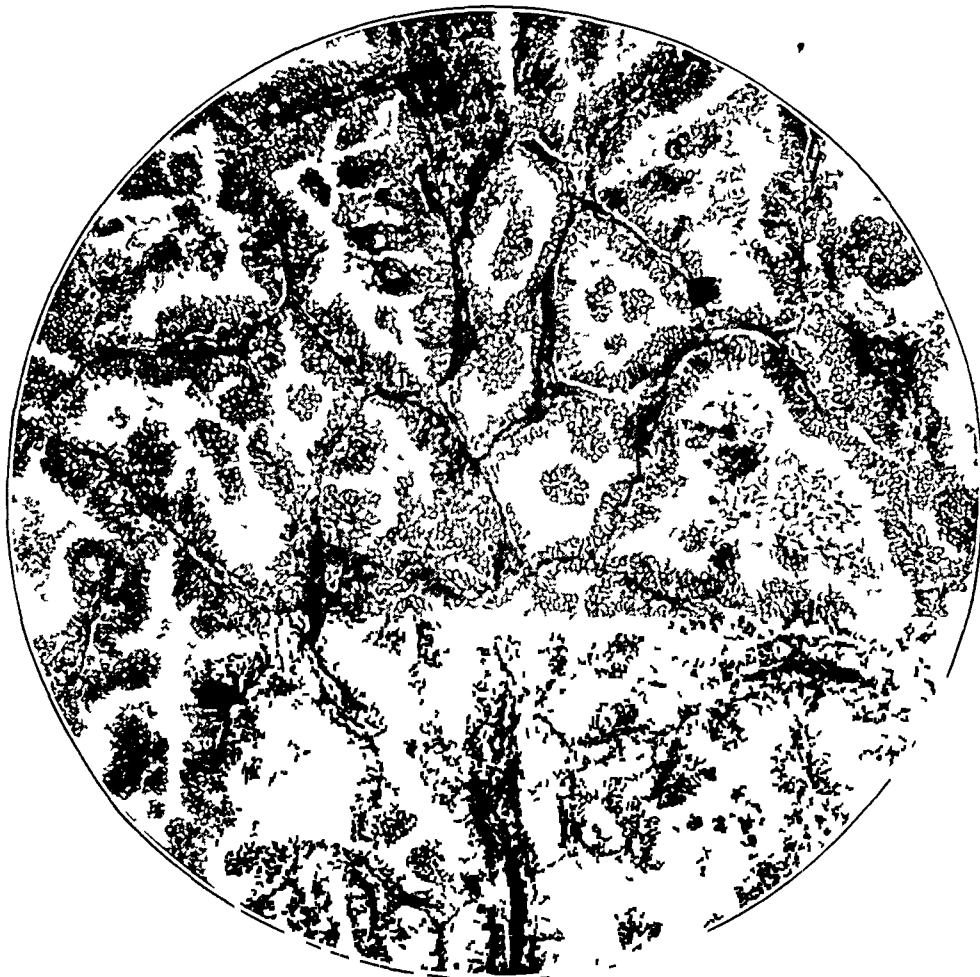


Fig 4—Section stained by Mallory's technic for connective tissue. Note that the basic structure of the alveolar wall is not greatly altered from normal except for the epithelial change and slight fibrosis ( $\times 45$  objective).

only numerous cocci, primarily in the pneumonic areas. No inclusion bodies could be found in either nuclei or cytoplasm.

Because of the bizarre and unfamiliar gross appearances, advantage was taken of frozen sections at the necropsy table. The tumor-like appearance of the tissue led to careful search for evidence of primary or metastatic neoplastic involvement elsewhere in the body, but none could be detected. The picture strongly suggested that described by Ewing<sup>6</sup> under the heading "Infectious Adenomatosis of Lungs in Sheep," in which he noted its supposed virus etiology. Consequently, portions of lung tissue were given to Dr. A. F. Rasmussen Jr., of the department of bacteriology of the University of Wisconsin, who attempted to transmit any causative virus by inoculating animals with a 10 per cent suspension of the tissue mass.

<sup>6</sup> Ewing, J. *Neoplastic Diseases*, ed 4, Philadelphia, W. B. Saunders Company, 1940, p. 874.

firm, on section moist, and pale gray mottled with black, they showed no apparent neoplastic change

On microscopic study the nodules seen grossly seemed to be formed by portions of lung tissue which retained their normal alveolar skeleton. The normal alveolar epithelium had been replaced by high cuboidal and columnar cells. Generally the alveoli were lined by only a single layer of cells, in one or two isolated spots there seemed to be a slight anaplastic tendency with the formation of tiny nests of polyhedral cells within an alveolar lumen. The cells were often so closely crowded together as to give a pseudostratified appearance, and in some areas they were pushed up into papillary folds supported on fine strands of stroma. An occasional mitotic figure was found in widely scattered areas. The epithelial cells themselves possessed granular cytoplasm, staining moderately heavily with eosin, and a large vesicular nucleus, usually located just below the middle of the cell but occasionally at either end. The

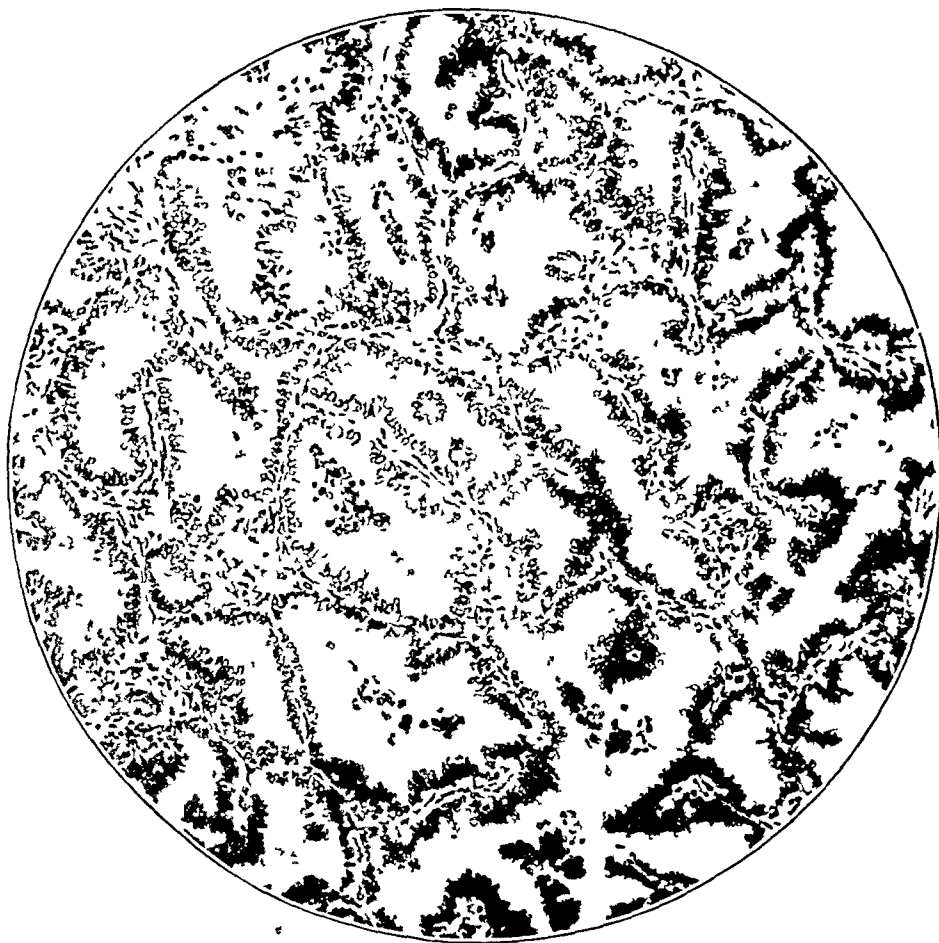


Fig 3—High power view ( $\times 45$  objective) of the nodule seen in figure 2. Hematoxylin and eosin stain.

nuclear membranes were quite heavy, and each nucleus contained one or two large nucleoli plus a few scattered chromatin threads and granules.

The stroma in general had the structure of the normal alveolar wall with slight fibrous thickening. In a few small areas interalveolar fibrosis was quite prominent, with bands of connective tissue as wide as the alveoli themselves. The vascular bed showed about the same degree of development as in normal pulmonary tissue, with no undue congestion. A few neutrophils and lymphocytes infiltrated the stroma, but this change was slight and no abnormal lymphoid accumulations were seen. A few laminated hyaline bodies, which were believed to be corpora amylacea, were noted. The involved alveoli contained small amounts of precipitated albuminoid material, with some mononuclear phagocytes, desquamated epithelial cells and an occasional neutrophil. There was little production of mucus in the adenomatous alveoli.

The areas of lung not involved by this process were mostly subject to an intense acute inflammatory edema and necrotizing bronchopneumonia of quite recent origin. The few small unaffected areas showed alternating patchy atelectasis and emphysema.

which seems identical with the present one and has discussed its possible relation to jagziekte. Still more recently Richardson<sup>12</sup> has briefly described an additional case which he feels is of this type. Bonne cited yet another report by Briese<sup>13</sup> of a seemingly related lesion, which, however, had metastasized to regional lymph nodes.

There seems to be a considerable gap between the lesions in such cases as these and the simple localized epithelial hyperplasia and metaplasia often seen as the result of the action on human lungs of infectious or irritant agents. It is possible that this gap is more apparent than real, and until considerably more is known about the genesis of the type of process in question it would be rash to venture an opinion on the point. One cannot, moreover, dismiss Grumbach's suggestion<sup>4</sup> that this type of change represents a nonspecific response to certain pulmonary irritants, in support of which he cited not only his own experiments but various pathologic descriptions of metaplasia of pulmonary epithelium. The close resemblance to jagziekte is suggestive, however, and Dungal, in a series of carefully conducted experiments, has shown clearly that that disease may be transmitted from sheep to sheep in the course of direct contact or by confinement of a healthy animal in a pen previously occupied by a diseased one. Attempts at artificial transmission of jagziekte by inoculation of affected tissue have been, with one possible exception, uniformly unsuccessful, as have efforts to find a causative bacterial agent (e. g., Dungal and Taylor<sup>14</sup>). Students of the disease seem increasingly to favor the hypothesis that a virus is the causative factor. If this belief is correct and if future observations confirm the parallelism of jagziekte in sheep with the lesions described as pulmonary adenomatosis in man, another hitherto unrecognized virus may be added to the list of infectious agents which can affect the human lung. Even more stimulating to speculation, if considered in connection with Dungal's demonstration of the transmissibility of the disease, is De Kock's<sup>15</sup> suggestion that jagziekte may represent a true neoplasm. His hypothesis would find some support in the metastases noted by Oberndorfer and Aynaud, as well as in the morphologic appearance of the tissues, but would require considerable additional evidence to be really tenable.

#### SUMMARY

A case of pulmonary adenomatosis in man resembling somewhat the disease jagziekte as found in sheep has been described. Current opinion suggests that jagziekte is an infectious disease, possibly of virus origin. A few similar human cases have been previously reported, so that it would seem that multiple bilateral pulmonary adenomas may occasionally develop in man, resembling morphologically those found in the ovine disease mentioned. While the evidence to support it is slight, there must be considered the possibility that this lesion as seen in sheep possesses neoplastic characteristics as well as transmissibility. The identity of the condition found in man with that found in sheep is not established by available evidence but further investigation seems indicated when opportunity presents.

12 Richardson, G. O. Adenomatosis of the Human Lung, *J. Path. & Bact.* **51** 297-298 (Sept.) 1940.

13 Briese. Zur Kenntnis des primären Lungenkarzinoms, mit statistischen Angaben, *Frankfurt Ztschr. f. Path.* **23** 48-55, 1920.

14 Dungal, N., and Taylor, E. L. Epizootic Adenomatosis in the Lungs of Sheep. Comparison with Jaagsiekte, Verminous Pneumonia and Progressive Pneumonia, *J. Comp. Path. & Therap.* **51** 46-68 (March 31) 1938.

15 de Kock, G. Are the Lesions of Jaagsiekte in Sheep of the Nature of a Neoplasm? *Ann. Rep. Dir. Vet. Serv. (sect. V-IX)* **2** 611-641, 1929, Further Observations on the Etiology of Jaagsiekte in Sheep, *ibid.* **2** 1169-1183, 1929.

which had been preserved in glycerin. One monkey received 6 cc intranasally under deep anesthesia induced with ether. Two rabbits received 3 cc each by intrapulmonic injection. Three guinea pigs were subjected to an atomized spray of 25 cc of the tumor suspension in a small closed chamber for a period of six hours. Intrapulmonic inoculations were made into other guinea pigs. Two of the guinea pigs died after about two months but showed no evidence of adenomatous pulmonary change. The other animals all remained well, and when they were put to death after some months' observation, no pulmonary adenomas or other apparently related lesions could be found. Facilities for the use of sheep were not available.

Dr E. V. Cowdry, who has made extensive studies of jagziekte and Montana progressive pneumonia of sheep, supplied us with several preparations from sheep lungs involved by jagziekte.

A comparison of those specimens with the involved tissues in our case emphasized their striking similarity in many respects. The pathologic changes in jagziekte have been repeatedly described in detail<sup>7</sup> and need not be reviewed here. The gross appearance, the basic histologic structure of the lesion, with retention of the normal pulmonary framework and total absence of destructive tendencies, the changes in the interstitial tissues, the absence of metastases and of invasion of the pleura or bronchi, the alveolar exudate and the epithelial hyperplasia described in the foregoing paragraphs are quite like those in the jagziekte sections available to us and those described in the literature. The individual epithelial cells in our case are not typical, however, those usually seen in jagziekte being less tall and having a somewhat clearer cytoplasm with a more darkly staining nucleus.

From the evidence available the lesions in the patient can be called only multiple pulmonary adenomatosis, and any suggestion as to their cause or their analogy to the changes of jagziekte in sheep must be purely speculative and without adequate support. The many parallel morphologic features and the absence of clearcut differentiating characteristics other than the dissimilarities in epithelial structure render such speculation tempting, however.

A few other isolated cases have been described in which the involvement corresponds more or less to the picture both in this patient and in sheep, while differing considerably from any other well known pulmonary lesion. Dungal<sup>7c</sup> reviewed the literature in search of such instances and cited reports by Lohlein,<sup>5</sup> Oberndorfer<sup>8</sup> and Helly.<sup>9</sup> The case of Helly seems almost identical with the present one except for a somewhat greater production of mucus in the affected alveoli. Oberndorfer's patient had very similar changes in the lungs, but metastases to bones and the regional nodes were present. (In this respect it may be noted that Aynaud,<sup>10</sup> whose sections were also studied by Dungal,<sup>7c</sup> found metastases in a single case of what was apparently true jagziekte in a sheep.) Lohlein's case histologically resembled Helly's but was limited to a single apple-sized tumor in the lower lobe of the right lung. In discussing Lohlein's report, Sternberg and Saltykow stated, without details, that they had each seen a somewhat similar tumor, while Oberndorfer also noted several reports by other workers of lesions possibly belonging to this group. Since Dungal's study, Bonne<sup>11</sup> has reported another case.

7 (a) Cowdry, E. V. Comparative Pathology of South African Jaagsiekte and Montana Progressive Pneumonia of Sheep, *J. Exper. Med.* **45** 571-585 (April) 1927, (b) Studies on the Etiology of Jaagsiekte, *ibid.* **42** 335-345 (Sept.) 1925. (c) Dungal, N. Epizootic Adenomatosis of the Lungs of Sheep. Its Relation to Vermineous Pneumonia and Jaagsiekte, *Proc. Roy. Soc. Med.* **31** 497-505 (March) 1938. Pallasse.<sup>2</sup>

8 Oberndorfer, S. Zellmutationen und multiple Geschwulstentstehungen in den Lungen, *Virchows Arch. f. path. Anat.* **275** 728-737, 1930.

9 Helly, K. Ein seltener primärer Lungentumor, *Ztschr. f. Heilk.* **28** 105-110, 1907.

10 Aynaud, M. Origine vermineuse du cancer pulmonaire de la brebis, *Compt. rend. Soc. de biol.* **95** 1540-1542, 1926.

11 Bonne, C. Morphological Resemblance of Pulmonary Adenomatosis (Jaagsiekte) in Sheep and Certain Cases of Cancer of the Lung in Man, *Am. J. Cancer* **35** 491-501 (April) 1939.

study by Macklin<sup>7</sup> showed the mechanism of transportation of air along sheaths of pulmonary blood vessels from alveoli to the mediastinum. Gumbiner and Cutter<sup>8</sup> have recently emphasized the making of lateral roentgenograms of the chest as a diagnostic procedure in cases of pneumomediastinum in newborn infants. Scadding and Wood<sup>9</sup> noted clicking and cracking sounds in 4 cases of spontaneous pneumothorax and clicking sounds in 2 cases of induced pneumothorax. These authors discounted mediastinal emphysema as a cause in their cases and attributed the sounds to forceful separation of pleural surfaces by cardiac systole.

In 1929 Dr. John Bainwell and I became interested in the mechanism of production of these sounds when we noted them in patients with induced pneumo-

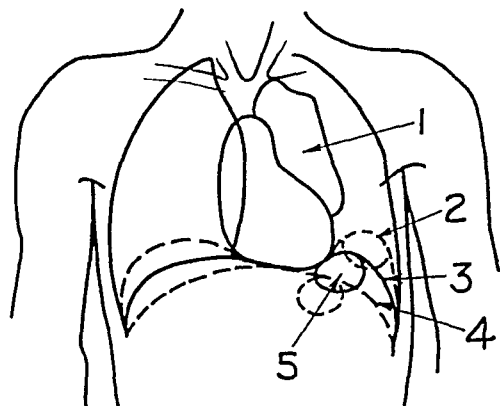


Fig 1—The diaphragm is in proper position during midinspiration and midexpiration for the heart to strike the gas bubble in the colon. 1, collapsed lung, 2, diaphragm during expiration, 3, diaphragm during midinspiration and midexpiration, 4, diaphragm during expiration, and 5, gas bubble in colon.

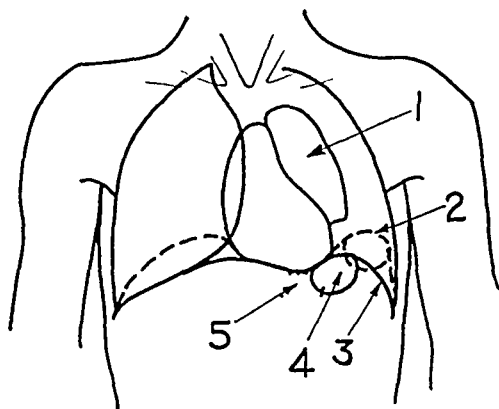


Fig 2—The diaphragm is in proper position during inspiration for the heart to strike the gas bubble in the colon. 1, collapsed lung, 2, diaphragm during expiration, 3, diaphragm during inspiration, 4, gas bubble in colon, and 5, gas bubble in stomach.

thorax on the left side. Several of our patients were disturbed by these sounds when they lay in various positions at different periods after the injection of air into the pleural cavity. One day during preparations to reintroduce air into one of these patients a loud knocking metallic sound began to emanate from the patient's

7 Macklin, C. C. Transport of Air Along Sheaths of Pulmonic Blood Vessels from Alveoli to Mediastinum. Clinical Implication, *Arch Int Med* **64** 913-926 (Nov.) 1939, Impediment to Circulation Occasioned by Pulmonic Interstitial Emphysema and Pneumomediastinum, *J Michigan M Soc* **39** 756-759 1940.

8 Gumbiner, B., and Cutter, M. M. Spontaneous Pneumomediastinum in the New Born, *J A M A* **117** 2050-2054 (Dec 13) 1941.

9 Scadding, J. G., and Wood, P. Systolic Click Due to Left-Sided Pneumothorax. *Lancet* **2** 1208-1211, 1939.



# UNUSUAL SOUNDS EMANATING FROM THE CHEST

CAUSE AND DIAGNOSTIC SIGNIFICANCE OF BUBBLING, CLICKING, CRUNCHING,  
KNOCKING AND TAPPING SOUNDS, WITH A REPORT OF TWO CASES  
OF INTERSTITIAL EMPHYSEMA OF LUNG AND MEDIASTINUM

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Bubbling, clicking, crunching, knocking and tapping sounds emanating from the chest are rarely encountered in civilian practice and their significance is not generally appreciated. With the current great military mobilization physicians will undoubtedly encounter these sounds in many instances of thoracic wounds in military personnel and in civilians. It appears pertinent, therefore, to emphasize their mechanism of production and their diagnostic significance.

Tapping, clicking and snapping metallic sounds were encountered by Rees and Hughes<sup>1</sup> and Smith<sup>2</sup> in soldiers with wounds of the left side of the chest during the last war. These sounds varied in intensity from ones audible only with the stethoscope applied over the precordium to those which could be heard 6 to 8 feet (183 to 244 cm.) from the patient. They were synchronous with the heart beat but varied in relation to the cardiac cycle. Some were audible only during systole, others only during diastole and others during both phases. They were related to respiration but varied also in their relation to the respiratory cycle. Some were heard or became louder during inspiration, others during expiration and others at midinspiration and midexpiration. It was thought by the original authors that a lesion of the left side of the chest was necessary. Munden<sup>3</sup> showed that these sounds were not peculiar to military personnel when he observed them in a civilian, and Lister<sup>4</sup> called attention to the importance of pneumothorax on the left side.

The diagnostic significance of these sounds is intimately associated with the mechanism of their production. The latter has been the subject of a good deal of debate. Smith<sup>2</sup> and Lister<sup>4</sup> attributed the sounds to the heart striking emphysematous blebs in the mediastinum, and in 1937 Hamman<sup>5</sup> reported 6 cases of spontaneous interstitial emphysema of the lung and mediastinum in which crunching and bubbling sounds were audible to both the patient and the physician. McGuire and Bean<sup>6</sup> later reported 2 more cases and gave an excellent review of the literature. Pneumothorax on the left side was present in some cases, but its presence was not necessary for the production of the sounds. An excellent

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1 Rees, W. A., and Hughes, G. S. Wounds of the Chest as Seen at an Advanced Operating Centre, *Lancet* **1** 55-59, 1918

2 Smith, S. M. Pericardial Knock, *Brit. M. J.* **1** 78, 1918

3 Munden, W. P. H. Pericardial Knock, *Brit. M. J.* **1** 174, 1918

4 Lister, W. A. Pericardial Knock Associated with Spontaneous Pneumothorax, *Lancet* **1** 1225-1226, 1928

5 Hamman, L. Spontaneous Interstitial Emphysema of the Lungs. *Tr. A. Am. Physicians* **52** 311-509, 1937

6 McGuire, J., and Bean, W. B. Spontaneous Interstitial Emphysema of the Lung. *Am. J. M. Sc.* **197** 502-509, 1939

sounds. It is to be noted that with the diaphragm at the normal level the sounds can be produced at midinspiration and midexpiration or at inspiration or at expiration. These sounds have been noted in association with varying degrees of collapse of the lung, from 25 to almost 100 per cent. The heart could strike an emphysematous bleb on the median aspect of a partially collapsed left lung and probably would produce a similar sound. It was thought that the mechanism of production of these sounds was due entirely to the process described here until similar sounds were heard in a case in which collapse of the lung was insufficient for the heart to strike the diaphragm and later in a case of pneumothorax on the right side. The sounds in these 2 cases, however, were different from the sounds previously observed. They were more clicking and tapping in character and were audible only with the stethoscope applied over the heart. It was thought therefore, that there were different causes for the different types of sounds. It was not until I observed the patient in case 1 that the mechanism of the second type of sounds which we had heard became clear.

#### REPORT OF CASES

CASE 1—A Negro physician aged 41 entered the University Hospitals on May 15, 1941, complaining of substernal pain and peculiar noises in his chest. He had enjoyed good health

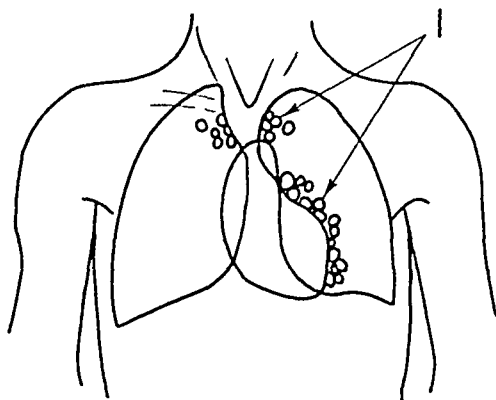


Fig 5—Interstitial emphysematous blebs (1) around the heart which cause bubbling, crunching and clicking sounds when they are struck by the heart

until about 9 p. m. May 9 when while sitting at his desk he was seized suddenly with substernal pain which was severe and radiated to the left shoulder. There was no accompanying shortness of breath, palpitation of the heart, pallor or perspiration. He went to bed immediately and noted that lying on the left side produced more pain and caused tapping, crunching and bubbling sounds to come from the chest. These sounds were audible to his wife at the bedside and were synchronous with the heart beat. He soon found that lying on the right side with a pillow beneath the thorax caused the pain and sounds to disappear promptly. A roentgenogram of the chest was obtained the next morning and revealed nothing abnormal. He remained in bed until six days later, when he was admitted to the hospital. During this time he was comfortable when lying on his right side, but the pain and sounds promptly returned when he turned on his back or his left side. Physical examination revealed no evidence of pneumothorax. The heart was normal, but tapping and clicking sounds were audible with the stethoscope placed anywhere over the precordium. They were systolic in time and were loudest during midinspiration and midexpiration. The foregoing data were obtained with the patient in the sitting and in the supine position. When he lay on the left side, they were crunching and bubbling in character and were continuous throughout respiration but continued to be systolic in time. An anteroposterior roentgenogram of the chest failed to reveal any abnormality, but an oblique roentgenogram revealed evidence of air in the mediastinum. The pain and the sounds gradually subsided until they disappeared ten days after onset. The temperature, pulse rate and leukocyte count were normal.

CASE 2—A white woman aged 21 entered the obstetric service of the University Hospitals on Jan. 4, 1942, for delivery of her second child after a full term pregnancy. During labor

chest. The sound was audible at a distance of 3 feet (91 cm), and several minutes later while I was listening with a stethoscope, borborygmus was heard and the sound disappeared. This occurred without introduction of more air into the pleural cavity or changing the position of the patient. It appeared likely therefore, that the sound was related to the presence of gas in the bowel. Such sounds were made to reappear in this patient and in another by the injection of air into the colon in amounts sufficient to distend the splenic flexure. In another patient observed fluoroscopically during the presence of such sounds it was noted that they occurred simultaneously with the heart striking the diaphragm immediately above a large bubble of gas in the splenic flexure of the colon. These sounds were of a knocking metallic character similar to those heard coming from the

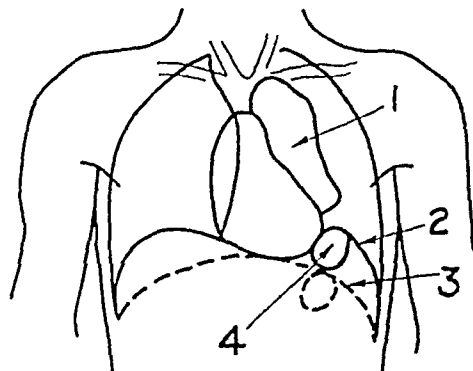


Fig 3—The diaphragm is in proper position during expiration for the heart to strike the gas bubble in the colon. 1 collapsed lung, 2, diaphragm during expiration, 3 diaphragm during inspiration, and 4 gas bubble in colon.

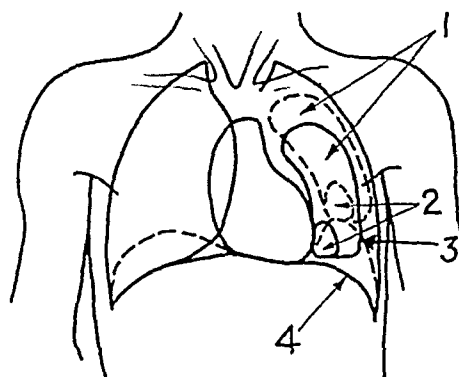


Fig 4—A large emphysematous bleb on the median aspect of the lung is in proper position to be struck by the uncushioned heart. 1 collapsed lung, 2 emphysematous bleb, 3, diaphragm during expiration, and 4, diaphragm during inspiration.

engine of a motor car during a hard pull. They were noted during systole in some instances and during diastole in others. They also occurred during different phases of respiration. If they were noted during inspiration, they persisted as long as inspiration was maintained. From our observation of several cases in which these sounds were noted at different times it appeared that those occurring during systole were due to rotation of the heart striking the diaphragm immediately above a bubble of gas in the colon. Those occurring during diastole were due to the fling of the uncushioned heart in diastole striking the diaphragm as just described. The relation to the respiratory phase depended on the height of the diaphragm and its relation to the heart. The accompanying diagrams illustrate the relations of the heart, the diaphragm and a gas bubble in the colon to the production of the

# VALUE OF SODIUM CHLORIDE IN PREVENTION OF ALKALOSIS DURING "SIPPY" TREATMENT WITH CALCIUM CARBONATE

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CHICAGO

Alkalosis can result from administration of soluble alkali<sup>1</sup> or from deprivation of chloride<sup>2</sup> or from both. It has been shown<sup>3</sup> also that the alkalosis observed during "Sippy" treatment with the administration of calcium carbonate is almost invariably associated with loss of gastric chloride and that in all probability the disturbance in the acid-base balance observed under these conditions is to be attributed to the loss of chloride rather than to calcium carbonate. If this thesis is correct, it should be possible to prevent the development of alkalosis by the administration of sodium chloride coincident with the administration of alkali. A study, therefore, was undertaken to determine the effect of the simultaneous administration of sodium chloride and calcium carbonate on the acid-base balance of a series of patients with peptic ulcer.

## METHOD

Sodium chloride and calcium carbonate were given concurrently to 150 patients with peptic ulcer. Eight patients were given minimal amounts of magnesium carbonate as a laxative. The series comprised 116 men and 34 women of ages ranging from 24 to 76. The serum carbon dioxide,  $p_H$  and chloride and the blood urea nitrogen were measured at various intervals during therapy.<sup>4</sup> Renal function was estimated by the urea clearance test.<sup>5</sup>

## RESULTS

*Acid-Base Balance*—The acid-base balance remained normal except for temporarily increased  $p_H$  values for 135 of the 150 patients (table 1). Alkalosis occurred in 15 patients (10 per cent). The serum carbon dioxide ranged from 32.9 to 41.0 millimols per liter, exceeding 40 millimols per liter in 2 instances. The  $p_H$  varied from 7.47 to 7.63. The lowest values for serum chloride ranged from 81.3 to 99.7 millimols per liter, the values of 6 patients were between 81.3 and 90 millimols per liter, and those of 9 patients exceeded 90 millimols per liter. The acid-base disturbance was arbitrarily classified as mild in 9 patients, moderate in 4 and severe in 2.

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From the Frank Billings Medical Clinic, Department of Medicine, University of Chicago.

1 Kirsner, J. B., and Palmer, W. L. Alkalosis Complicating the Sippy Treatment of Peptic Ulcer, *Arch Int Med* **69** 789 (May) 1942.

2 Kirsner, J. B., and Knowlton, K. Acid-Base Balance, Renal Function and Gastric Secretion During Hypochloremia in the Dog, *J Clin Investigation* **20** 303 (May) 1941.  
Kirsner, J. B., Palmer, W. L., and Knowlton, K. Studies on Experimental and Clinical Hypochloremia in Man, *J Clin Investigation* **22** 95 (Jan) 1943.

3 Kirsner, J. B., and Palmer, W. L. The Role of Chlorides in Alkalosis Following the Administration of Calcium Carbonate, *J A M A* **116** 384 (Feb 1) 1941.

4 Peters, J. P., and Van Slyke, D. D. Quantitative Clinical Chemistry, Baltimore, Williams & Wilkins Company, 1931, vol 2. Serum CO<sub>2</sub>, p 283,  $p_H$  (Colorimetric), p 796, Chloride, p 835, Blood Urea Nitrogen, p 554.

5 Van Slyke, D. D., and others. Observations on the Courses of Different Types of Bright's Disease and on Resultant Changes in Renal Anatomy, *Medicine* **9** 257 (Sept) 1930.

on January 16 she strained forcefully with each uterine contraction, and during the latter part of labor she experienced a sharp pain over the precordium. The pain was not severe but prevented her from straining as hard as previously. The labor was normal, and she delivered a 7 pound (3,175 Gm) normal baby. Immediately after labor a slight swelling and crepitation were noted in the neck by the attending physician. The heart sounds were distant, and synchronously with systole and diastole crackling sounds were heard which persisted when respiration was stopped. Approximately two hours later these sounds were crunching and bubbling in character, continued throughout the respiratory phase and were both systolic and diastolic in time. They became louder when the patient was turned on the left side, but at no time were they audible without application of the stethoscope to the precordium. The crepitation in the neck and the sounds gradually decreased, with the latter changing to tapping and clicking sounds before they disappeared five days after onset. There were no systemic reactions, and the patient was discharged on the tenth day post partum.

#### COMMENT

The clicking and tapping sounds in the 2 cases reported here were identical with those heard in the last 2 cases of pericardial knock associated with pneumothorax observed by Barnwell and myself. The crunching and bubbling sounds were not observed in the previous cases. In the 2 cases reported here pneumothorax was not present, and the sounds were typical of those occurring in interstitial emphysema of the lung and mediastinum. The bubbling, crunching, clicking and tapping sounds in these 2 cases were due undoubtedly to the heart striking emphysematous blebs in the lung and mediastinum. It appears logical from the data at hand to assume that the bubbling and crunching sounds are produced by fairly numerous or fairly large emphysematous blebs in close proximity to the heart, whereas clicking and tapping sounds are due to smaller and to less numerous blebs in the same vicinity. The knocking sounds, on the other hand, and probably some of the tapping sounds are produced by the heart striking a larger bubble of air located a little farther from the heart and separated from it by air free in the pleural cavity. The bubble of air may be an emphysematous bleb on the median aspect of a partially collapsed left lung or a gas bubble in the splenic flexure of the colon immediately beneath the diaphragm. The bubble must be at the proper distance from the heart to be struck an optimum blow by the rotation of the heart during systole or by the free diastolic fling of the uncushioned heart.

The clinical significance of these sounds has been discussed in part with the mechanism of production. Their occurrence indicates that interstitial emphysema of the lung or mediastinum or pneumothorax of the left side is present. The available data indicate that knocking or tapping metallic sounds occur in cases of pneumothorax of the left side, whereas bubbling, crunching and clicking sounds occur in cases of interstitial emphysema of the lung and mediastinum. These conditions may occur spontaneously, but they are usually due to trauma and they frequently coexist.

#### SUMMARY

Two cases of interstitial emphysema of the lung and mediastinum, spontaneous in 1 case and following straining in normal labor in the other, are reported. It is concluded that the bubbling, crunching, clicking and some of the tapping sounds are due to the heart rubbing against emphysematous blebs in interstitial emphysema of the lung and mediastinum. The knocking and tapping metallic sounds, on the other hand, are due to the heart striking an emphysematous bleb on the median aspect of a partially collapsed left lung or the diaphragm immediately over a gas bubble in the splenic flexure of the colon in the presence of pneumothorax of the left side. These conditions may occur spontaneously, or they may be due to trauma.

*Blood Urea Nitrogen*—The blood urea nitrogen increased during alkalosis in 10 patients. The maximum values for 6 ranged from 16.2 to 30 mg per hundred cubic centimeters and for 4 from 35.8 to 97 mg per hundred cubic centimeters. The highest value for blood urea nitrogen (97 mg per hundred cubic centimeters) was that of a 66 year old man with hypertension and urinary retention secondary to prostatic obstruction. Hypertension was present in the 4 patients with the highest values for blood urea nitrogen. The urine of 4 patients undergoing treatment contained slight to moderate amounts of albumin and hyaline and granular casts. Albumin and casts were present in the urine of 1 of these patients before treatment.

TABLE 3—*Urea Clearance During Therapy with Sodium Chloride and Calcium Carbonate*

Urea Clearance	No Alkalosis	Alkalosis
Unchanged	92	2
Reduced	8	8
Undetermined	35	5
Totals	135	15

TABLE 4—*Gastric Retention*

Volume (Cc)	No Alkalosis	Alkalosis
0-100	81	0
100-200	30	3
200-300	12	3
300-400	9	2
400-500	1	5
500	2	2
Totals	135	15

TABLE 5—*pH of Urine Before and After Administration of Sodium Chloride to Six Normal Infants\**

Before	After
5.80	7.35
6.75	6.40
6.75	7.10
6.35	6.75
5.90	6.00

\* Data taken from Schoenthal.<sup>7</sup>

*Gastric Retention*—A significant difference existed between the patients with normal serum electrolytes and those in whom alkalosis developed with respect to the volume of gastric contents aspirated daily (table 4). The amount aspirated averaged less than 200 cc for 111 (81 per cent) of the patients without alkalosis but for only 3 (20 per cent) of those with alkalosis. Large quantities of acid gastric juice thus were removed daily from 12 (80 per cent) of the patients in whom alkalosis occurred. The loss of chloride via gastric aspiration appeared to be of considerable importance in the pathogenesis of hypochloremia and alkalosis, since in these persons presumably from 0.5 to 2.0 Gm of chloride ion contained in the gastric contents, as well as a considerable portion of the sodium chloride given orally, was thereby removed each day. In view of the absence of changes in the serum electrolytes in some patients in whom marked gastric retention also was

*Clinical Aspects*—No direct relation existed between the amount of calcium carbonate ingested and the development of alkalosis. The total alkali intake of the 135 patients with normal serum electrolytes ranged from 200 to 500 Gm for 104 patients and from 500 to 1,000 Gm for 27 patients. The remaining 4 patients of this group received 1,148, 1,154, 1,850 and 2,355 Gm of calcium carbonate, respectively. The total alkali intake of the patients in whom alkalosis developed varied from 200 to 500 Gm for 9 patients and from 500 to 1,000 Gm for 2 patients, 4 patients received 1,080, 1,144, 1,305 and 2,897 Gm, respectively. There was likewise no correlation between the amount of alkali given and the severity of the acid-base disturbance, for the alkalosis was mild in 3 of the 4 patients receiving the largest amounts of calcium carbonate.

Nine of the 15 patients with alkalosis did not have any complaints referable to the acid-base disturbance. The symptoms of the other 6 patients consisted of weakness, nausea, headache, dizziness and mental confusion.

In the group with normal serum electrolytes 9 patients had had massive hemorrhage, 9 had hypertension and 1 had polycythemia rubra vera. Other complica-

TABLE 1—*Acid-Base Balance During Simultaneous Administration of Sodium Chloride and Calcium Carbonate (One Hundred and Fifty Patients)*

	Serum CO <sub>2</sub> (mM/L)	Serum pH	Serum Cl (mM/L)
No alkalosis (135 patients)	22.30	7.35-7.50	95-105
Alkalosis (15 patients)	32.0-41.0	7.47-7.63	81.3-99.7

TABLE 2—*Urea Clearance at Beginning of Therapy with Sodium Chloride and Calcium Carbonate*

Urea Clearance	No. Alkalosis	Alkalosis
Normal	94	4
Below normal	21	5
Undetermined	20	6
Totals	135	15

tions in the group with alkalosis consisted of massive hemorrhage (3), hypertension (6), persistent secondary anemia (1) and perforated ulcer with diabetes (1).

*Renal Function*—Of the patients in whom alkalosis did not develop, the urea clearance of 94 at the beginning of treatment was normal, that of 21 was below normal and that of 20 was undetermined. Renal function of 8 patients in this group decreased temporarily during combined therapy with sodium chloride and calcium carbonate, originally, the urea clearance of 6 patients had been normal and that of 2 had been below normal.

In the group of patients in whom alkalosis developed the urea clearance at the onset of treatment was normal for 4, impaired for 5 and undetermined for 6 (table 2). Renal function during alkalosis was not altered significantly in 2 patients whose urea clearance had been normal originally. Renal function diminished during alkalosis in 8 patients, the clearance of 4 of them was below normal at the beginning of therapy. The values in 5 instances dropped to levels as low as 7, 11, 15, 19, and 20 per cent of average normal. The urea clearance subsequently returned to its original level in 7 of the 8 patients (undetermined for 1) in whom it had decreased. Renal function of 5 patients was not measured during alkalosis (table 3).

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anemic Renal function was not measured prior to alkali therapy. A total of 390 Gm of calcium carbonate was given in seventeen days. Gastric contents obtained by aspiration averaged 220 cc daily. Mild chemical alkalosis was noted on the third day of therapy, the acid-base disturbance became severe on the fifteenth day, at which time the blood urea nitrogen rose to 27 mg per hundred cubic centimeters and the urea clearance decreased to 20 per cent of average normal. In addition to the 10 Gm of sodium chloride taken by mouth daily large amounts of physiologic solution of sodium chloride were given parenterally on the third, the seventh, the sixteenth, the seventeenth and the eighteenth day of therapy. The acid-base balance on the twenty-second day was normal despite continued ingestion of alkali. Three weeks later, the blood urea nitrogen measured 13.5 mg per hundred cubic centimeters and the urea clearance was 70 per cent of average normal.

CASE 7—P. L., a 40 year old man with a stenosing duodenal ulcer and hypertension, was found on admission to be in a state of mild alkalosis. The acid-base balance was restored to normal after three infusions of 1,500 cc of physiologic solution of sodium chloride. A total of 414 Gm of calcium carbonate was given subsequently. Gastric contents obtained by aspiration averaged 800 cc daily. Eight grams of sodium chloride was given by mouth daily. Mild chemical alkalosis was noted on the seventh day of alkali therapy, but the serum electrolytes returned to normal without additional treatment.

CASE 8—F. S., a 54 year old man with a stenosing duodenal ulcer, had moderately severe alkalosis on the fourth day of alkali treatment. Gastric contents obtained by aspiration had averaged 490 cc daily. Renal function was not measured prior to therapy; during alkalosis, however, the urea clearance was only slightly below normal. The acid-base balance was partially restored after the intake of sodium chloride by mouth had been increased from 5 to 15 Gm daily and physiologic solution of sodium chloride had been administered on the fourth and the fifth day of treatment. "Tri-calsate" was substituted for calcium carbonate on the fourteenth day of therapy, and the serum electrolytes returned to normal. The blood urea nitrogen and the urea clearance were normal after subsidence of the alkalosis.

CASE 9—F. O. T., a 53 year old man with syphilis and hypertension, had vomited frequently prior to admission to the hospital. A total of 328 Gm of calcium carbonate was given in eleven days. Gastric contents obtained by aspiration averaged 195 cc daily. Renal function was not measured prior to alkali therapy. Mild chemical alkalosis was noted on the ninth day of therapy, the blood urea nitrogen increased to 24.8 mg per hundred cubic centimeters, and the urea clearance dropped to 10 per cent of average normal. Alkali therapy was discontinued for three days, and the daily intake of sodium chloride was increased from 5 to 10 Gm. 3,000 and 1,300 cc of physiologic solution of sodium chloride were administered parenterally on two occasions. The acid-base balance returned to normal and was not altered after the resumption of calcium carbonate therapy.

CASE 10—J. McI., a 41 year old man with syphilis and hypertension, had taken large amounts of sodium bicarbonate for the relief of symptoms of ulcer. On entry, the blood urea nitrogen measured 23.3 mg per hundred cubic centimeters and the urea clearance 60 per cent of average normal. A total of 212 Gm of calcium carbonate was given during the first seventeen days, 3 Gm of sodium chloride was taken by mouth daily. Gastric contents obtained by aspiration averaged 230 cc daily. Moderately severe alkalosis was noted on the sixth day of treatment. The blood urea nitrogen measured 29.8 mg per hundred cubic centimeters and the urea clearance 22 per cent. From 1,500 to 3,000 cc of physiologic solution of sodium chloride was given daily from the sixth to the tenth day of therapy. Calcium carbonate therapy was discontinued, and aluminum hydroxide alone was administered during the next sixteen days. The acid-base balance returned to normal, although the blood urea nitrogen continued to range from 18.2 to 27.0 mg per hundred cubic centimeters. Calcium carbonate therapy was resumed on the thirty-fourth day of hospitalization, 6 Gm of sodium chloride was given by mouth daily. The serum electrolytes remained normal except for a slight elevation of the serum carbon dioxide (32.8 millimols per liter). One month later, the blood urea nitrogen measured 20.7 mg per hundred cubic centimeters and the urea clearance 40 per cent of average normal.

CASE 11—T. D., a 66 year old man, entered the hospital because of a massive hemorrhage from a duodenal ulcer. Seven blood transfusions and 1,144 Gm of calcium carbonate were administered in twenty-nine days. Five grams of sodium chloride was given by mouth daily. The clinical course was complicated by the development of urinary retention. Mild

6 Tri-calsate is a proprietary antacid which when in aqueous solution consists essentially of tribasic calcium phosphate and sodium citrate.

present and whose intake of sodium chloride was no greater than that of patients with alkalosis, it would seem that the loss of chloride in the group with alkalosis had not been completely replaced by therapy with salt

*Sodium Chloride Therapy*—Of the patients in whom alkalosis did not develop, the daily intake of sodium chloride (in addition to the salt in the diet) averaged 4 to 5 Gm for 61 patients and 5 to 10 Gm for 74 patients. The daily intake of sodium chloride of the 15 patients in whom alkalosis developed averaged 3 to 5 Gm for 7 patients and 5 to 10 Gm for 8 patients

#### SUMMARY OF FIFTEEN CASES OF ALKALOSIS OCCURRING DURING ANTACID THERAPY

CASE 1—A F, a 31 year old man with a stenosing duodenal ulcer, was found on admission to have a serum carbon dioxide of 33 millimols per liter. The blood urea nitrogen and the urea clearance were normal. There was moderately severe secondary anemia. Gastric contents obtained by aspiration averaged 457 cc daily. Mild alkalosis was detected on the thirteenth day of treatment, the urea clearance decreased moderately during the acid-base disturbance. The serum electrolytes and the renal function returned to normal after the daily intake of sodium chloride (5 to 8 Gm) had been increased to 10 Gm.

CASE 2—A J, a 43 year old man, received a total of 2,897 Gm of calcium carbonate in forty-eight days. Gastric aspirations over a period of forty-one days averaged 400 cc daily. Mild chemical alkalosis was noted on the twentieth day of therapy, the urea clearance was normal. The intake of sodium chloride (3 to 5 Gm) was increased to 10 Gm daily, and the acid-base balance returned to normal in seven days.

CASE 3—G K, a 39 year old man with diabetes and a large gastric ulcer, was first treated by continuous Wangenstein aspiration of the gastric contents for six days. The serum electrolytes were maintained by parenteral injections of physiologic solution of sodium chloride. A total of 1,305 Gm of calcium carbonate was administered in the succeeding forty-four days, 10 Gm of sodium chloride was given by mouth daily. The blood urea nitrogen and the urea clearance were normal prior to alkali therapy. Mild chemical alkalosis was noted on the thirteenth and the twenty-third day of hospitalization (the seventh and the seventeenth day of alkali therapy). The blood urea nitrogen and the urea clearance remained normal, however. Despite the continuation of alkali therapy the acid-base balance returned to normal.

CASE 4—S M, a 43 year old man, received a total of 588 Gm of calcium carbonate in twenty days. Gastric contents obtained by aspiration over a period of eighteen days averaged 400 cc daily. The original value for urea clearance was slightly reduced. Moderate alkalosis was noted on the sixth day of treatment, the patient had been vomiting for two days previously. The acid-base disturbance became severe on the twelfth day, the blood urea nitrogen increased to 174 mg per hundred cubic centimeters, and the urea clearance fell to 43 per cent of average normal. The daily intake of sodium chloride (4 to 8 Gm) was increased to 10 Gm, and on the fourteenth day 200 cc of a 2 per cent solution of sodium chloride was given intravenously, calcium carbonate therapy was continued. The serum electrolytes and the blood urea nitrogen returned to normal in seven days, the urea clearance simultaneously returned to its original level.

CASE 5—L L, a 45 year old man with hypertension, was placed on antacid therapy ten days before entry into the hospital and on admission was found to be in a state of mild alkalosis. The blood urea nitrogen three weeks previously had measured 21.4 mg per hundred cubic centimeters, the urea clearance was not determined. The alkalosis became moderately severe after six days, at which time the blood urea nitrogen had risen to 50 mg per hundred cubic centimeters and the urea clearance had decreased to 20 per cent of average normal. Gastric contents obtained by aspiration over a period of fourteen days had averaged 328 cc daily. The intake of sodium chloride (3 to 5 Gm) was increased to 10 Gm daily, and 5 per cent dextrose in physiologic solution of sodium chloride was given parenterally for two days, calcium carbonate therapy was continued. The acid-base balance was restored approximately to normal in five days. Three and one-half months later, despite continued alkali therapy, the serum electrolytes were normal, the blood urea nitrogen measured 10.8 mg per hundred cubic centimeters, and the urea clearance was 65 per cent of average normal.

CASE 6—D H S, a 53 year old man with hypertension, had experienced a massive hemorrhage from a duodenal ulcer shortly before admission to the hospital. He was markedly

chloride, but this did not equal the intake. These data are in agreement with the observations of Gyorgy<sup>9</sup> in his study of excretion of acid by infants after the administration of sodium chloride.

It should be noted that in several patients of the present series sodium chloride therapy was apparently not only inadequate to forestall the development of alkalosis but insufficient to correct the acid-base disturbance. It is possible that to these few patients insufficient amounts of salt were given and also that the excretion of bicarbonate in the urine was retarded by antecedent impairment of renal function.

#### CONCLUSIONS

Administration of sodium chloride during "Sippy" treatment with calcium carbonate decreased the incidence of alkalosis from 30 to 10 per cent.

This type of alkalosis is due to the loss of chloride (gastric aspiration) and can be prevented by the administration of sufficient amounts of sodium chloride.

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<sup>9</sup> Gyorgy, P. Zur Frage der Saureausscheidung im Urin, *Ztschr f d ges exper Med* **43** 443, 1924.

alkalosis was noted on the second day. The alkalosis became severe on the twenty-sixth day. At this time, the blood urea nitrogen rose to 97 mg per hundred cubic centimeters and the urea clearance diminished to 7 per cent of average normal (renal function had been impaired originally). Gastric contents obtained by aspiration between the twenty-first and the thirty-first day averaged 502 cc daily. The serum electrolytes returned to normal after the daily administration of 3,000 cc of 5 per cent dextrose in physiologic solution of sodium chloride and of saline solution alone. Alkali therapy and gastric aspiration were discontinued on the thirty-first day of hospitalization. The blood urea nitrogen gradually decreased to 12.8 mg per hundred cubic centimeters, and the urea clearance one month later rose to 60 per cent of average normal, its original level.

CASE 12—F C, a 48 year old man with hypertension, was admitted to the hospital with a massive hemorrhage from a duodenal ulcer. A total of 734 Gm of calcium carbonate was given in twenty-nine days. Gastric contents obtained by aspiration averaged 168 cc. daily. Before treatment urea clearance was slightly below normal. Symptoms suggestive of alkalosis were noted on the twenty-fourth day of hospitalization, at which time the daily intake of sodium chloride (3 to 6 Gm) was increased to 10 Gm. Mild chemical alkalosis was noted on the twenty-sixth day, and 1,500 cc of physiologic solution of sodium chloride was given parenterally. Calcium carbonate therapy was discontinued on the thirtieth day, at which time the blood urea nitrogen measured 31.2 mg per hundred cubic centimeters and the urea clearance 15 per cent of average normal. The blood urea nitrogen returned to normal and the urea clearance to its original level several weeks later.

CASE 13—L B, a 48 year old man, had been vomiting frequently for six to seven months. The urea clearance was not determined before alkali therapy was begun. Gastric contents obtained by aspiration over a period of twenty days averaged 300 cc daily. Severe alkalosis was noted on the ninth day of therapy, the daily intake of sodium chloride was increased from 5 to 8 Gm, with prompt clinical relief.

CASE 14—H F, a 55 year old man, had vomited frequently before hospitalization. Large amounts of gastric contents were aspirated daily. The original value for urea clearance was low. Mild alkalosis was noted on the eleventh day. The intake of sodium chloride was maintained at a level of 10 Gm daily. There were no clinical symptoms. The acid-base balance was not determined subsequently.

CASE 15—J G, a 44 year old man with normal renal function, was found to have mild chemical alkalosis on the eighth day of alkali therapy. The serum electrolytes were not measured subsequently. There were no clinical symptoms.

#### COMMENT

The results of this investigation indicate that alkalosis complicating "Sippy" treatment with calcium carbonate can be prevented in almost all patients by the concurrent administration of adequate amounts of sodium chloride. The therapeutic action of sodium chloride is probably attributable (a) to the replacement of chloride ion lost by the aspiration of gastric contents and (b) to the increased excretion of base bicarbonate in the urine at the expense of the blood bicarbonate after the administration of salt. The experimental observations of Schoenthal<sup>7</sup> are of particular importance in this connection. Hartmann and Smyth<sup>8</sup> had shown previously that in the presence of an increased level of plasma bicarbonate secondary to loss of chloride the administration of sodium chloride leads to the excretion of bicarbonate in the urine. Schoenthal gave 6 healthy infants 6 to 10 Gm of sodium chloride daily, distributed equally in the feedings over a period of one to four days. An increase in the chloride concentration of the serum of 6 to 15 per cent was observed in all infants. The plasma bicarbonate decreased moderately in 4 infants, and the reaction of the plasma of 3 infants tended to shift toward the acid side. The excretion of base bicarbonate in the urine was usually increased and accompanied by a rise in  $pH$ , as shown in table 5. There was naturally an increase in the urinary

<sup>7</sup> Schoenthal, L. Acid-Base Metabolism. Effects of Administration of Salt and of Restitution of Water, *Am J Dis Child* **37** 244 (Feb.) 1929.

<sup>8</sup> Hartmann, A. F., and Smyth, F. S. Chemical Changes in the Body Occurring as a Result of Vomiting, *Am J Dis Child* **32** 1 (July) 1926.

pyridoxine, pantothenic acid and ascorbic acid, when administered for four to six weeks, did not have any effects, favorable or otherwise, on brief extreme exercise, on prolonged severe exercise and in semistarvation on the muscular ability of these previously well nourished persons. It was found that the young men expending an average of 4,200 calories per day were not benefited by a daily supply of more than 17 mg of thiamine hydrochloride, 24 mg of riboflavin and 70 mg of ascorbic acid. The investigators concluded that no useful purpose would be served by enrichment of the present garrison rations of the United States Army with the vitamins studied.

In the industrial field Schnedorf and his associates<sup>3</sup> were unable to find much evidence for vitamin deficiency disease in a survey of 1,265 healthy men. On the other hand, preliminary surveys made by a committee of the National Research Council<sup>4</sup> revealed deplorable conditions among persons engaged in war work in many plants. The following recommendations were made:

1. Nutritious meals of natural foods at prices the workers are accustomed to and can afford to pay should be made available in all plants engaged in production for war or defense purposes, except in small plants where the worker may obtain such meals from private sources in the free time at his disposal. Any meal served in the plant should contribute at least one-third of the daily requirements of specific nutrients recommended by the Food and Nutrition Board of the National Research Council.

2. The practice of serving food between meals to workers has given good results and is recommended. Milk, fruit and tomato juices are to be preferred as beverages, and other foods which are served should include the necessary nutrients. Thus, when bread is served it should be enriched white bread or a whole grain product.

3. Choice of foods served in the plant should be determined by a trained dietitian or nutritionist. Brief study of workers' diets will enable the dietitian to make up menus calculated to compensate for the ordinary inadequacies. The employment of a dietitian or nutritionist by the plant is recommended. In cases where this is not feasible, advice may be obtained from the state or local Committee on Nutrition.

4. Suitable educational material should be presented in connection with cafeteria service or supplementary lunches to stimulate acceptance of the meals planned or the selection of good meals when there is a choice of foods. Such material should be so planned as to lead to the development of good health habits and should avoid undue emphasis on any particular food.

5. Measures should be taken by the appropriate subdivision of government to condition nutritionally those classes of the population which are likely to become workers in war or defense industries. Such nutritional conditioning might well be carried out among organized groups such as are found in CCC camps, NYA, WPA and Defense Training Schools. The large percentage of young men found to be unfit for service in the armed forces emphasizes the need for such conditioning, for employment in war industries may be just as strenuous and in far less favorable environment than service in the armed forces. Such work, already under way in this country, should be greatly extended.

The observation was reported<sup>5</sup> that administration of the vitamin B complex improved the working capacity in occupations in which fatigue, attributable to fatigue of the central nervous system, occurred. However, the Council on Foods and Nutrition and the Council on Industrial Health of the American Medical Association pointed out<sup>6</sup> that satisfactory evidence is lacking of the wisdom of the general practice of industrial concerns of indiscriminately providing all of their

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3 Schnedorf, J. G., Weber, C. J., and Clendenning, L. A Vitamin Survey of Normal Industrial Workmen, *Am J Digest Dis* **9** 188-191 (June) 1942.

4 The Food and Nutrition of Industrial Workers in Wartime, Committee on Nutrition in Industry, National Research Council, Reprint and Circular Series, no 110, April 1942.

5 Simonson, E., Enzer, N., Baer, A., and Braun, R. The Influence of Vitamin B (Complex) Surplus on the Capacity for Muscular and Mental Work, *J Indust Hyg & Toxicol* **24** 83-90 (April) 1942.

6 Indiscriminate Administration of Vitamins to Workers in Industry, report of the Council on Foods and Nutrition and the Council on Industrial Health, *J A M A* **118** 618-621 (Feb 21) 1942.

# Progress in Internal Medicine

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## DISEASES OF NUTRITION

REVIEW OF CERTAIN RECENT CONTRIBUTIONS

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Because of the pressure of work occasioned by the war this year's review on diseases of nutrition must be abbreviated. It represents, in fact, little more than a compilation of casual reading in the field. Important items undoubtedly have escaped attention.

We are happy to be able to inform our readers of the appearance in November 1942 of the first issue of a new journal called *Nutrition Reviews*. This publication has been undertaken by the recently created Nutrition Foundation, Inc., New York. The editorial staff of the new journal has been carefully selected and justifies the confidence of members of the medical profession and other persons engaged in application of nutritional knowledge. Issues will appear monthly. It is proposed to bridge the gap between substantial research findings and their acceptance on the part of those persons who have responsibility for application of the best of what is new. The reviews must be critical in their appraisals of material if this purpose is to be accomplished, and to judge from the contents of the first issue critical appraisal can be expected. The subscription price is nominal. Much of the literature on nutrition is not to be found in journals which customarily are available to physicians. The issues of *Nutrition Reviews* as they appear are intended to provide authoritative, unbiased, editorially interpreted reviews of the world's progress in the science of nutrition and since this science applies to almost every field of medicine, *Nutrition Reviews* should be a welcome addition to the libraries of physicians.

### GENERAL PROBLEMS

With the coming of war the nutritional problems of the armed forces, the industrial workers and the general populace have assumed critical importance. The nutritional problems of the Army have received much attention.<sup>1</sup> In an excellent paper Keys and Henschel<sup>2</sup> reported a comprehensive study made on a group of soldiers from the United States Army to determine the effect of various vitamin supplements on muscular ability, endurance, resistance to fatigue and recovery from fatigue. It was found that thiamine, riboflavin, niacin (nicotinic acid),

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1 Tobey, J. A. The Army's Nutritional Problems, *War Med* **2** 437-444 (May) 1942  
Howe, P. E. Nutritional Problems of the Army, *Mil Surgeon* **90** 253-266 (March) 1942  
Epstein, M. H. The Nutrition of the Soldier, *ibid* **89** 872-877 (Dec) 1941

2 Keys, A., and Henschel, A. F. Vitamin Supplementation of U. S. Army Rations in Relation to Fatigue and the Ability to Do Muscular Work, *J. Nutrition* **23** 259-269 (March) 1942

to human beings, 88 to 96 per cent of it failed to be accounted for in the blood and the feces. However, after ingestion of large doses of vitamin A a substance was found in the blood and the feces which seemed to be a closely related oxidation product<sup>13</sup>

Feller and his associates,<sup>14</sup> in a critical study of the influence of vitamin A and vitamin C on immunologic reactions in human beings, found little to support the view that vitamin A or ascorbic acid affects so-called "resistance to infection"

*Methods of Measuring Vitamin A Deficiency*—The controversy on the value of measuring deficiency of vitamin A by dark adaptation tests continues. However, the opinion that the test of adaptation to darkness does not sharply identify cases of mild vitamin A deficiency is gaining favor.<sup>15</sup> With refinements in methods of measuring vitamin A in the blood have come studies which indicate that this method is more sensitive as an indicator of vitamin A deficiency. It seems to be promising, although more data are needed to establish the range of normal and of abnormal values.<sup>16</sup> Yudkin<sup>17</sup> reported that both alcohol and amphetamine sulfate may produce transient improvement in adaptation to darkness without any corresponding increase in the concentration of vitamin A in the blood. Kruse<sup>15c</sup> refutes the charge that changes in adaptation to darkness preceded conjunctival changes noted by him in many cases of vitamin A deficiency. In more than 100 persons who did not have impaired adaptation to darkness he observed gross or microscopic changes in the conjunctivas. These changes slowly disappeared after administration of vitamin A. As was mentioned in last year's review, Kruse maintained that under ordinary conditions conjunctival changes probably precede dysadaptation in avitaminosis A.

*Clinical Deficiencies*—A summary of the clinical conditions associated with vitamin A deficiency was published by Mandelbaum.<sup>18</sup> Administration of vitamin A in doses of 25,000 to 50,000 international units daily for three to eight weeks was reported to have enabled color-blind patients to pass a standard color vision test in which they previously had failed.<sup>19</sup> The permanence of this improvement remained to be determined. The levels of vitamin A in the plasma of patients with cancer of the gastrointestinal tract were found to be below the normal range in 86

13 LePage, G. A., and Pett, L. B. Absorption Experiments with Vitamin A, *J. Biol. Chem.* **141**:747-761 (Dec.) 1941

14 Feller, A. E., Roberts, L. B., Ralli, E. P., and Francis, T., Jr. Studies on the Influence of Vitamin A and Vitamin C on Certain Immunological Reactions in Man, *J. Clin. Investigation* **21**:121-137 (March) 1942

15 (a) Oldham, H., Roberts, L. J., MacLennan, K., and Schultz, F. W. Dark Adaptation of Children in Relation to Dietary Levels of Vitamin A, *J. Pediat.* **20**:740-752 (June) 1942. (b) Hunt, E. P., and Hayden, K. M. Medical Evaluation of Nutritional Status. IX. The Reliability of Visual Threshold During Dark Adaptation as a Measure of Vitamin A Deficiency in a Population Group of Low Income, *Milbank Memorial Fund Quart.* **20**:139-168 (April) 1942. (c) Kruse, H. D. Methods of Detecting Mild Cases of Vitamin A Deficiency, *Science* **95**:623-624 (June 19) 1942

16 Bodansky, O., Lewis, J. M., and Haig, C. The Comparative Value of the Blood Plasma Vitamin A Concentration and the Dark Adaptation as a Criterion of Vitamin A Deficiency, *Science* **94**:370-371 (Oct. 17) 1941. Lewis, J. M., Bodansky, O., and Haig, C. Level of Vitamin A in the Blood as an Index of Vitamin A Deficiency in Infants and in Children, *Am. J. Dis. Child.* **62**:1129-1148 (Dec.) 1941. Yarbrough, M. E., and Dann, W. J. Dark Adaptometer and Blood Vitamin A Measurements in a North Carolina Nutrition Survey, *J. Nutrition* **22**:597-607 (Dec.) 1941

17 Yudkin, S. Vitamin A and Dark-Adaptation Effect of Alcohol, Benzedrine and Vitamin C, *Lancet* **2**:787-791 (Dec. 27) 1941

18 Mandelbaum, J. Vitamin A. Some Clinical Considerations, *M. Clin. North America* **26**:965-984 (May) 1942

19 Dunlap, K., and Loken, R. D. Vitamin A for Color-Blindness, *Science* **95**:554 (May 29) 1942



employees with vitamins. This report emphasized the need for avoidance of the indiscriminate mass use of vitamins, a practice which supports commercial exploitation rather than scientific rational use of these important dietary factors.

The civilian population is beset with nutritional problems. From a rather extensive survey Jolliffe, McLester and Sherman<sup>7</sup> concluded that dietary inadequacies and malnutrition of varying degrees are of frequent occurrence in the United States and that the nutritional status of an appreciable part of the population can be distinctly improved. They pointed out that if optimal nutrition, not merely adequate nutrition, is sought, then widespread improvement is possible.

As clearly pointed out by Ruffin,<sup>8</sup> both the public and the members of the medical profession have become overenthusiastic on the subject of vitamins, and there is a rapidly growing tendency today to attribute most of the ills of the human race to vitamin deficiency. This author emphasized that when specific deficiencies occur, response to specific therapy is rapid, and if the patient does not show any improvement after three or four weeks of treatment, there seems little justification in allowing him to buy preparations of vitamins, especially those containing the vitamin B complex. In his experience treatment of patients suspected of having a mild deficiency with single members of the vitamin B complex have been most disappointing. In a recent editorial<sup>9</sup> the use of many so-called "shotgun" vitamin preparations was condemned. On the other hand, the Council on Foods and Nutrition of the American Medical Association<sup>10</sup> has approved and will accept for listing in New and Nonofficial Remedies multivitamin preparations in which the proportions of the various vitamins included bear a direct relation either to the minimal requirements promulgated by the Food and Drug Administration or to the recommended daily allowances of the Food and Nutrition Board of the National Research Council. A multivitamin preparation used by the armed forces as a dietary supplement in emergencies, when rations may be inadequate, contains vitamin A 2,500 international units, vitamin D 200 U. S. P. units, vitamin B<sub>1</sub> 1 mg., riboflavin 1.5 mg., niacin amide 10 mg. and ascorbic acid 37.5 mg. These values represent approximately half the daily recommended allowances of the Food and Nutrition Board for men consuming 3,000 calories of food.

During the past year several reviews on various phases of nutrition have appeared and bear reading.<sup>11</sup>

#### VITAMIN A

*Chemistry and Physiology*—The excretion of vitamin A appears to be highly selective. Lawrie and his associates<sup>12</sup> reported that vitamin A is associated in urine with only minute amounts of lipoids. In human urine vitamin A is absent in health but present in association with some pathologic conditions, particularly pneumonia, chronic nephritis and nephrosis. In pneumonia the daily excretion of vitamin A sometimes exceeds 3,000 international units. When vitamin A was given orally

7 Jolliffe, N., McLester, J. S., and Sherman, H. C. The Prevalence of Malnutrition, *J. A. M. A.* **118** 944-950 (March 21) 1942.

8 Ruffin, J. M. The Diagnosis and Treatment of Mild Vitamin Deficiencies. A Clinical Discussion, *J. A. M. A.* **117** 1493-1496 (Nov. 1) 1941.

9 Shotgun Vitamins Rampant, editorial, *J. A. M. A.* **117** 1447 (Oct. 25) 1941.

10 The Proper Use of Vitamins in Mixtures, report of the Council on Pharmacy and Chemistry and Council on Foods and Nutrition, *J. A. M. A.* **119** 948-949 (July 18) 1942.

11 Williams, R. J. The Approximate Vitamin Requirements of Human Beings, *J. A. M. A.* **119** 1-3 (May 2) 1942. Starr, P. The Value of Vitamins in Surgical Practice. Collective Reviews, *Internat. Abstr. Surg.* **74** 309-322 (April) 1942. Jeghers, H. Nutrition, *New England J. Med.* **225** 687-697 (Oct. 30) 1941. Gyorgy, P. The Water-Soluble Vitamins, *Ann. Rev. Biochem.* **11** 309-364, 1942.

12 Lawrie, N. R., Moore, T., and Rajagopal, K. R. Excretion of Vitamin A in Urine, *Biochem. J.* **35** 825-836, 1941.

leukemia is not followed by any increase in the pyrimidine content of leukocytes, although normal amounts of both thiamine and pyrimidine are excreted in the urine<sup>28</sup>

Appraisals of methods for measuring thiamine in blood and in urine and a discussion of their possible value in determining the nutritional status of human beings were published in the last year<sup>29</sup>

Raw cow's milk contains 41 to 48 micrograms of thiamine hydrochloride per hundred cubic centimeters, pasteurization leads to losses of 10 to 20 per cent. Evaporated milk contains 18 to 27 micrograms per hundred cubic centimeters. Early in the lactating period human milk contains much less thiamine than cow's milk<sup>30</sup>. The thiamine content gradually increases until about the twelfth week of the period, after which it remains almost constant<sup>31</sup>. It also has been reported<sup>32</sup> that thiamine is excreted in sweat. A man may lose from 2 to 3 Kg of weight daily in sweat without visible perspiration and thus may lose a significant amount of thiamine. It was suggested that a person performing hard labor in a high environmental temperature may lose enough thiamine to have serious consequences.

Development of a syndrome simulating Wernicke's disease has been encountered in foxes fed a diet containing raw carp. Further study of the problem revealed that this is due to inactivation of a specific vitamin by a constituent of carp. The substance apparently is not present in the muscle of the carp but in the skin, scales, skeleton, head and viscera. It is destroyed by cooking. Large amounts of thiamine must be mixed with the raw fish to prevent the syndrome, but if the thiamine is given at a time when it will not be mixed with the fish, either in the feed pan or in the gastrointestinal tract, only a small amount is needed to prevent development of the syndrome. The possibility that other dietary constituents may destroy a given vitamin or in some way cause a normally adequate supply of that vitamin to become insufficient demands consideration both in human and in veterinary medicine<sup>33</sup>. Macht and Spencer<sup>34</sup> described interactions between cobra venom and thiamine.

*Clinical Studies*—Severe restriction of thiamine is associated with progressive inactivity, apathy, derangement of metabolic processes and loss of weight finally

28 Abels, J. C., Gorham, A. T., Craver, L., and Rhoads, C. P. The Measurement and Metabolism of Thiamin and of a Pyrimidine Stimulating Yeast Fermentation Found in the Blood Cells and Urine of Patients with Leukemia, *J Clin Investigation* **21** 177-189 (March) 1942

29 Harris, L. J., and Wang, Y. L. Vitamin Methods. I. An Improved Procedure for Estimating Vitamin B<sub>1</sub> in Foodstuffs and Biological Materials by the Thiochrome Test Including Comparisons with Biological Assays, *Biochem J* **35** 1050-1067, 1941. Egaña, E., and Meiklejohn, A. P. The Estimation of Thiamine in Urine, *J Biol Chem* **141** 859-870 (Dec) 1941. Youmans, J. B., Patton, E. W., and Sutton, W. R. The Clinical Significance of Blood Thiamin (Fermentation Method) Values, *Tr A Am Physicians* **56** 377-383, 1941. Kirch, E. R., and Bergeim, O. The Chemical Determination of Thiamine, *J Biol Chem* **143** 575-588 (May) 1942. Stotz, E., and Bessey, O. A. The Blood Lactate-Pyruvate Relation and Its Use in Experimental Thiamine Deficiency in Pigeons, *ibid* **143** 625-631 (May) 1942. Mason, H. L., and Williams, R. D. The Urinary Excretion of Thiamine as an Index of the Nutritional Level. Assessment of the Value of a Test Dose, *J Clin Investigation* **21** 247-255 (March) 1942.

30 Kendall, N. Thiamin Content of Various Milks, *J Pediat* **20** 65-73 (Jan) 1942.

31 Slater, E. C., and Rial, E. J. The Thiamin (Vitamin B<sub>1</sub>) Content of Human Milk, *M J Australia* **1** 3-12 (Jan 3) 1942.

32 Hardt, L. L., and Still, E. U. Thiamin in Sweat, *Proc Soc Exper Biol & Med* **48** 704-707 (Dec) 1941.

33 Green, R. G., Carlson, W. E., and Evans, C. A. The Inactivation of Vitamin B<sub>1</sub> in Diets Containing Whole Fish, *J Nutrition* **23** 165-174 (Feb) 1942.

34 Macht, D. I., and Spencer, E. C. Pharmacological Interactions of Cobra Venom and Thiamine, *J Am Pharm A (Scient Ed)* **31** 146-150 (May) 1942.

per cent<sup>20</sup> Although administration of yeast and of lipocaic, which are free of carotenoids, raised the levels of vitamin A in the plasma of these patients, hepatic dysfunction was not believed to be the cause of the low levels<sup>21</sup> Absorption of vitamin A by patients who have pulmonary tuberculosis also is impaired,<sup>22</sup> but the derangements of function responsible are not known

The intimate and important role of the liver in metabolism of vitamin A continues to be emphasized<sup>23</sup> It has long been known that an injured hepatic parenchyma contains less vitamin A than normal hepatic parenchyma and is less able to handle carotenoid metabolism It is reported that abnormal adaptation to darkness was exhibited in 90 per cent of a group of 20 cases of cirrhosis of the liver, although clinical night blindness was present in only 16 per cent<sup>24</sup> The level of vitamin A in the blood of 90 per cent of patients with cirrhosis of the liver and of carotenoid in the blood of 50 per cent of them was below the lowest normal values<sup>25</sup> A large dose of vitamin A (100,000 international units) administered to a patient with cirrhosis of the liver is said to be followed by a smaller rise in the plasma level of vitamin A than occurs in a normal subject<sup>26</sup> A test of this type may serve as an index of vitamin A deficiency in a patient with disease of the liver

#### THIAMINE

*Chemical and Physiologic Properties*—The average level of thiamine in the normal leukocyte was reported to be ten times that in the normal erythrocyte<sup>27</sup> a distribution similar to that of riboflavin and of ascorbic acid The greater concentrations in leukocytes may be explained by the fact that these cells are more actively metabolizing tissue than the other components of blood An increase in urinary excretion of pyrimidine follows the parenteral administration of thiamine, and it is believed that this substance is derived from thiamine Evidence also was presented to show that thiamine is broken down to pyrimidine in the course of its metabolism in leukocytes After intravenous administration of thiamine to normal persons a significant increase in the concentration of pyrimidine in the blood cells and the urine occurs However, administration of thiamine to persons with

20 Abels, J C , Gorham, A T , Pack, G T , and Rhoads, C P Metabolic Studies in Patients with Cancer of the Gastro-Intestinal Tract I Plasma Vitamin A Levels in Patients with Malignant Neoplastic Disease, Particularly of the Gastro-Intestinal Tract, *J Clin Investigation* **20** 749-764 (Nov ) 1941

21 Abels, J C , Gorham, A T , Pack, G T , and Rhoads, C P Metabolic Studies in Patients with Gastrointestinal Cancer III The Hepatic Concentrations of Vitamin A, *Proc Soc Exper Biol & Med* **48** 488-492 (Nov ) 1941

22 Breese, B B , Jr , Watkins, E , and McCord, A B The Absorption of Vitamin A in Tuberculosis, *J A M A* **119** 3-4 (May 2) 1942

23 Haig, C , and Post, J Vitamin A Concentration in Rat Liver During Recovery from CCl<sub>4</sub> Cirrhosis, *Proc Soc Exper Biol & Med* **48** 710-714 (Dec ) 1941

24 Wohl, M G , and Feldman, J B The Occurrence of Avitaminosis A in Diseases of the Liver, *Am J Digest Dis* **8** 464-469 (Dec ) 1941

25 Haig, C , and Patek, A J , Jr Vitamin A Deficiency in Laennec's Cirrhosis The Relative Significance of the Plasma Vitamin A and Carotenoid Levels and the Dark Adaptation Time, *J Clin Investigation* **21** 309-317 (May) 1942 Stewart, J D , and Rourke, G M Vitamin A Content of Plasma and Hepatic Tissue Biopsied at Operation Effects of Pre-operative Therapy in Obstructive Jaundice, *Surgery* **11** 939-948 (June) 1942 Oldham, Roberts, MacLennan and Schultz<sup>15a</sup>

26 Ralli, E P , Bauman, E , and Roberts, L B The Plasma Levels of Vitamin A After the Ingestion of Standard Doses Studies in Normal Subjects and Patients with Cirrhosis of the Liver, *J Clin Investigation* **20** 709-713 (Nov ) 1941

27 Gorham, A T , Abels, J C , Robins, A L , and Rhoads, C P The Measurement and Metabolism of Thiamin and of a Pyrimidine Stimulating Yeast Fermentation Found in the Blood Cells and Urine of Normal Individuals, *J Clin Investigation* **21** 161-176 (March) 1942

A review of the literature on untoward reactions to thiamine hydrochloride was published recently, and 2 more cases of sensitivity to this compound were added to the literature <sup>45</sup> It is interesting that in these cases the patients were able to tolerate the vitamin when it was administered orally and yet showed definite allergic reactions after parenteral administration It has been suggested that cutaneous testing of patients about to receive thiamine hydrochloride parenterally be made as a precautionary measure However, the report by Kalz <sup>46</sup> did not fully confirm this advice Kalz injected thiamine hydrochloride intradermally into 30 patients and a histamine-like reaction consisting of an urticarial wheal with a surrounding erythematous area from 3 to 6 cm in diameter occurred in all It was suggested that thiamine hydrochloride is an obligate wheal-producing substance and therefore positive intradermal tests with it are not conclusive proof of an individual subject's sensitivity

#### NIACIN

*Chemistry and Physiology*—The Food and Nutrition Board of the National Research Council recently selected niacin and niacin amide as suitable synonyms for nicotinic acid and nicotinic acid amide The Council on Foods and Nutrition of the American Medical Association accepted these synonyms <sup>47</sup>

Trigonelline and nicotinuric acid are the two known end products of the metabolism of nicotinic acid encountered in urine of human beings In an excellent study by Sarett and his associates <sup>48</sup> 10 mg of known niacin derivative was found in the urine daily, regardless of diet After oral administration of a 200 mg dose of niacin 25 to 90 mg could be accounted for by the increase of 55 to 84 per cent in urinary trigonelline and of 16 to 45 per cent in urinary nicotinuric acid Interestingly enough, trigonelline is not utilized by human beings when taken orally and is excreted almost completely without change About 60 per cent of nicotinuric acid ingested is excreted unchanged and without an accompanying increase in trigonelline

Further studies on the metabolism of niacin have been made by Najjar and associates, <sup>49</sup> who described the presence in the urine of certain fluorescent substances which varied in a characteristic way in pellagra One of these, designated "F<sub>1</sub>," occurred in relatively small amounts in normal urine but in large quantities in the urine of pellagrins The second substance, designated "F<sub>2</sub>," present in normal urine was increased in amount when niacin was administered The second substance was not encountered usually in the urine of pellagrins but appeared after administration of niacin The urinary excretion of both substances was followed in dogs with experimental niacin deficiency, and observations on these animals are in agreement with those made on human beings with pellagra Acute niacin deficiency is followed by a disappearance of excretion of the second substance and an increase in excretion of the first substance, as the disease becomes chronic, even the excretion of the first substance tends to fall

45 Eisenstadt, W S Hypersensitivity to Thiamine Hydrochloride, *Minnesota Med* **25** 861-863 (Nov) 1942

46 Kalz, F Thiamine Hydrochloride—An Obligate Wheal Producing Agent, *J Invest Dermat* **5** 135-137 (June) 1942

47 Niacin and Nicotinic Acid, editorial, *J A M A* **118** 823 (March 7) 1942

48 Sarett, H P, Huff, J W, and Perlzweig, W A Studies in Nicotinic Acid Metabolism I The Fate of Nicotinic Acid in Man, *J Nutrition* **23** 23-24 (Jan) 1942

49 Najjar, V A, Stern, H J, Holt, L E, Jr, and Kabler, C V The Excretion of Specific Fluorescent Substances in the Urine in Experimental Nicotinic Acid Deficiency, *J Clin Investigation* **21** 263-267 (May) 1942

ending in prostration. In all cases of induced deficiency of thiamine mental and physical inefficiency preceded by weeks or months other more objective manifestations. With further studies of this problem Williams and his associates<sup>35</sup> found the optimal intake of thiamine hydrochloride for human beings to be not less than 0.5 mg or more than 1.0 mg for each 1,000 calories of a diet providing carbohydrates and fats in conventional proportions.

Low concentrations of thiamine in the blood were encountered frequently in alcoholic addicts who presented acute peripheral neuropathy.<sup>36</sup> Machella and Elsom<sup>37</sup> did not find any essential difference in the percentage of ingested thiamine excreted in the urine of the control subjects and that excreted in the urine of patients with hepatic disease receiving a basal diet. However, when such a diet was supplemented with thiamine, patients with hepatic disease excreted less thiamine than did the controls. These authors suggested that impairment of intestinal absorption may result from hepatic disease.

A critical review of the use of thiamine in the treatment of nerve deafness and tinnitus appeared.<sup>38</sup> The authors did not find any conclusive evidence in favor of the use of this vitamin for this purpose. Thiamine was claimed to be of some value in the treatment of "dry socket"<sup>39</sup> and oral leukoplakia,<sup>40</sup> and its use in eclampsia was suggested.<sup>41</sup>

Observations reported by Smith and Mason<sup>42</sup> failed to provide any grounds for the assumption that the level of intake of thiamine influenced either the intensity of diabetes or the sensitivity to the action of insulin. The relatively mild degree of depression of tolerance for carbohydrate which has been encountered in intact animals and human beings after long periods of deprivation of thiamine appears to represent a disturbance of metabolism unrelated to that involved in diabetes mellitus. Such "false diabetes" is correctable by administration of thiamine, the same is not true of diabetes mellitus. The administration of large doses of vitamin B complex for sixteen weeks to diabetic patients was reported not to have had any discernible effect on the severity of the disease,<sup>43</sup> and thiamine has been found not to be of any help in treatment of protracted diabetic coma or insulin shock.<sup>44</sup>

35 Williams, R. D., Mason, H. L., Smith, B. F., and Wilder, R. M. Induced Thiamine (Vitamin B<sub>1</sub>) Deficiency and the Thiamine Requirement of Man. Further Observations, *Arch Int Med* **69** 721-738 (May) 1942.

36 Goodhart, R. The Thiamin Content of Human Blood and Urine as Determined by the Fermentation Method, *J Clin Investigation* **20** 625-630 (Nov.) 1941.

37 Machella, T. E., and Elsom, K. O. Studies of the B Vitamins in the Human Subject. Urinary Excretion of Ingested Thiamine in Patients with Chronic Hepatic Disease, *Am J M Sc* **202** 512-516 (Oct.) 1941.

38 Shambaugh, G. E., Jr., and Jennes, M. L. Therapy of Nerve Deafness and Tinnitus Aurium. Use of Large Doses of Thiamine Hydrochloride and Evaluation of Results, with a Source of Possible Error in Interpretation of Improvement, *Arch Otolaryng* **35** 513-522 (April) 1942.

39 Osterloh, J. P. Thiamine Hydrochloride in the Treatment of "Dry Socket," *J Am Dent A* **29** 1445-1446 (Aug. 1) 1942.

40 Abels, J. C., Rekers, P. E., Martin, H., and Rhoads, C. P. The Relationship Between Dietary Deficiency and the Occurrence of Papillary Atrophy of the Tongue and Oral Leukoplakia, *Cancer Research* **2** 381-393 (June) 1942.

41 Nixon, W. C. W., Wright, M. D., and Fieller, E. C. Vitamin B<sub>1</sub> in the Urine and Placenta in Toxaemia of Pregnancy, *Brit M J* **1** 605-607 (May 16) 1942.

42 Smith, K. A., and Mason, H. L. Thiamin and Diabetes Mellitus, *Proc Staff Meet, Mayo Clin* **15** 529-532 (Aug. 21) 1940.

43 Robson, G. B., Cutting, W. C., and Gray, H. Effect of the Vitamin B Complex in Diabetes Mellitus, *J Clin Endocrinol* **2** 262-263 (April) 1942.

44 Somerfeld-Ziskind, E., Ziskind, E., Dalton, L., and Buck, V. Vitamin B<sub>1</sub> Not Helpful in Protracted Insulin Shock, *Am J M Sc* **203** 110-114 (Jan.) 1942.

Meller<sup>58</sup> reported that in 4 cases of postencephalitic paralysis agitans improvement did not occur after treatment with pyridoxine but in 6 cases of idiopathic paralysis agitans this type of therapy decreased pain and rigidity and increased general well-being. Keith<sup>59</sup> did not note any benefit in the treatment with pyridoxine of pseudohypertrophic muscular dystrophy among children.

Jolliffe and his associates<sup>60</sup> have reported some success in treatment of persistent postadolescent acne vulgaris. From 50 to 250 mg of pyridoxine was given orally each day in divided doses. Of 37 patients, 9 were cleared of the disease and 19 were improved. Of the control group of 35 patients given starch and sugar tablets, 7 were improved.

#### PANTOTHENIC ACID

It has been suggested that pantothenic acid may be involved in the regulation of water metabolism,<sup>61</sup> and recent experimental data suggest that this substance is required for maintaining the integrity of the adrenal cortex.<sup>62</sup> It may be of some interest to know that honey contains pantothenic acid<sup>63</sup> and that royal jelly, a secretion of the pharyngeal glands of worker honey bees, is reported to be the richest known source of this substance. On a dry basis royal jelly contains an average of 511 micrograms of pantothenic acid per gram, this is between two and a half and six times as much as is present in yeast or liver.<sup>64</sup>

A few clinical studies of pantothenic acid have appeared. Wright and Wright<sup>65</sup> reported on the urinary excretion of pantothenic acid of 29 normal persons. The mean daily excretion was 342 mg in twenty-four hours. These results compare favorably with those reported by Pelzar and Porter, mentioned in last year's review. The daily urinary excretion of pantothenic acid by patients with pernicious anemia does not indicate impairment of absorption of this compound.<sup>66</sup> It is known that in rats with experimentally produced hyperthyroidism administration of thiamine will arrest loss of weight but that lost weight is not regained until a rich source of the vitamin B complex, such as yeast, is added to the diet. Drill and Overman<sup>67</sup> reported that pyridoxine and calcium pantothenate can effectively replace yeast in such experiments and that, like thiamine, these substances are required in greater amounts during hyperthyroidism.

58 Meller, C. L. Ten Cases of Paralysis Agitans Treated with Vitamin B<sub>6</sub>, *Minnesota Med* **25** 22-24 (Jan) 1942.

59 Keith, H. M. Vitamin B<sub>6</sub> (Pyridoxine Hydrochloride) in the Treatment of Pseudo-hypertrophic Muscular Dystrophy Among Children, *J. Pediat* **20** 200-207 (Feb) 1942.

60 Jolliffe, N., Rosenblum, L. A., and Sawhill, J. The Effects of Pyridoxine (Vitamin B<sub>6</sub>) on Persistent Adolescent Acne, *J. Invest. Dermat* **5** 143-148 (June) 1942.

61 Figge, F. H. J., and Atkinson, W. B. Relation of Water Metabolism to Porphyrin Incrustations in Pantothenic Acid-Deficient Rats, *Proc. Soc. Exper. Biol. & Med* **48** 112-114 (Oct) 1941.

62 Supplee, G. C., Bender, R. C., and Kahlenberg, O. J. Interrelated Vitamin Requirements: Kidney Damage, Adrenal Hemorrhage and Cardiac Failure Correlated with Inadequacy of Pantothenic Acid, *Endocrinology* **30** 355-364 (March) 1942.

63 Haydak, M. H., Palmer, L. S., Tanquary, M. C., and Vivino, A. E. Vitamin Content of Honeys, *J. Nutrition* **23** 581-588 (June) 1942.

64 Pearson, P. B., and Burgin, C. J. The Pantothenic Acid Content of Royal Jelly, *Proc. Soc. Exper. Biol. & Med* **48** 415-417 (Nov) 1941.

65 Wright, L. D., and Wright, E. Q. Urinary Excretion of Pantothenic Acid by Normal Individuals, *Proc. Soc. Exper. Biol. & Med* **49** 80-81 (Jan) 1942.

66 Meyer, C. E., Burton, I. F., and Sturgis, C. C. Pantothenic Acid Absorption in Pernicious Anemia, *Proc. Soc. Exper. Biol. & Med* **49** 363-365 (March) 1942.

67 Drill, V. A., and Overman, R. Increased Requirements of Pantothenic Acid and Vitamin B<sub>6</sub> During Experimental Hyperthyroidism, *Am. J. Physiol* **135** 474-477 (Jan) 1942.

Further studies on the distribution of niacin in foods were reported<sup>50</sup> All animal tissue contains niacin, but the liver and the kidney are the richest sources<sup>51</sup> Cooking and commercial processing apparently cause some loss of the vitamin New methods for measuring niacin in animal tissues and blood were reported,<sup>52</sup> and a method for determining niacin deficiency in human beings was described<sup>53</sup>

*Clinical Use*—Manson-Bahr<sup>54</sup> advanced the hypothesis that the syndrome of sprue is mainly the result of nonabsorption or destruction of factors of vitamin B<sub>2</sub> complex in the small intestine He administered orally 150 mg of niacin each day for fourteen days of each month for six months At the end of this time the patient was improved markedly Intensive parenteral liver therapy was continued, however, in conjunction with this specific treatment

It is well known that niacin has a vasodilating action and because of this fact its use in the treatment of asthma has been suggested<sup>55</sup> Twenty-one patients in asthmatic paroxysms received intravenously 0.1 Gm of niacin, and of these 21, 11 had relief within three to five minutes after the injection The relief seemed to coincide with the appearance of a flush, which is a common reaction following parenteral use of niacin The duration of the relief lasted from a few to fifteen hours Nine patients were given oral doses of 0.2 Gm before each meal Five of these 9 patients were benefited

#### RIBOFLAVIN

No new important clinical advances in knowledge of this vitamin have come to our attention Machella<sup>56</sup> reported healing of cheilosis in 9 of 13 patients receiving pyridoxine The remaining few patients failed to respond either to riboflavin or to pyridoxine, but 1 of them responded to nicotinic acid Other investigators also have noted that cheilosis in some cases heals only when the entire vitamin B complex in the form of liver extract and brewers' yeast is supplied These observations indicate that cheilosis is not necessarily a manifestation of riboflavin deficiency alone

New laboratory methods for measuring riboflavin deficiency in human beings appeared within the year<sup>57</sup>

#### PYRIDOXINE

The controversy concerning the effectiveness of pyridoxine in the treatment of neuromuscular diseases is lessening The results of treatment are not encouraging

50 Teply, L. J., Strong, F. M., and Elvehjem, C. A. The Distribution of Nicotinic Acid in Foods, *J. Nutrition* **23** 417-423 (April) 1942

51 McIntire, J. M., Waisman, H. A., Henderson, L. M., and Elvehjem, C. A. Nicotinic Acid Content of Meat and Meat Products, *J. Nutrition* **22** 535-540 (Nov.) 1941

52 Giri, K. V., and Naganna, B. An Adsorption Method for the Estimation of Nicotinic Acid Content of Animal Tissues and Blood, *Indian J. M. Research* **29** 585-590 (July) 1941  
Jones, W. S. Photoelectric Determination of Nicotinic Acid, *J. Am. Pharm. A. (Scient. Ed.)* **30** 272-275 (Oct.) 1941

53 Perlzweig, W. A., Sarett, H. P., and Margolis, L. H. Studies in Nicotinic Acid Metabolism. V. A Test for Nicotinic Acid Deficiency in Man, *J. A. M. A.* **118** 28-30 (Jan. 3) 1942

54 Manson-Bahr, P. The Treatment of Sprue with Vitamin B<sub>2</sub> and Its Bearing upon the Aetiology of This Disease, *Tr. Roy. Soc. Trop. Med. & Hyg.* **34** 347-372 (March) 1941

55 Maisel, F. E., and Somkin, E. Treatment of Asthmatic Paroxysms with Nicotinic Acid. Preliminary Report, *J. Allergy* **13** 397-403 (May) 1942

56 Machella, T. E. Studies of the B Vitamins in Human Subjects. III. The Response of Cheilosis to Vitamin Therapy, *Am. J. M. Sc.* **203** 114-120 (Jan.) 1942

57 Jones, W. S., and Christensen, W. G. Fluorophotometric Determinations of Riboflavin. *J. Am. Pharm. A. (Scient. Ed.)* **30** 270-272 (Oct.) 1941  
Najjar, V. A. The Fluorometric Determination of Riboflavin in Urine and Other Biological Fluids, *J. Biol. Chem.* **141** 355-364 (Nov.) 1941  
Najjar, V. A., and Holt, L. E., Jr. A Riboflavin Excretion Test as a Measure of Riboflavin Deficiency in Man, *Bull. Johns Hopkins Hosp.* **69** 476-481 (Nov.) 1941

(dopa) 2 Further oxidation of this compound is prevented by hydrogen acceptance of ascorbic acid 3 Melanin is transformed by ascorbic acid into less deeply colored products

Several new methods for measuring ascorbic acid were reported and criticized <sup>73</sup>

*Clinical Use*—An excellent and complete summary of the metabolism of ascorbic acid in adult scurvy has been published within the year,<sup>74</sup> and a good review of the subject of scurvy in children also was reported, together with the presentation of 15 new cases encountered in children less than 12 years of age <sup>75</sup> Some authors have maintained that the hemorrhagic features of scurvy are due to a deficiency of vitamin P In an attempt to settle this question Cameron and Mills <sup>76</sup> gave vitamin P but not ascorbic acid to a patient who had classic scurvy The hemorrhagic features disappeared promptly, although other features of the disease were unaffected until ascorbic acid was added

The ascorbic acid requirements of premature infants <sup>77</sup> and school children <sup>78</sup> have been reported, and it has been shown rather definitely that children who receive 3 ounces (90 cc) or more of orange juice daily or an equivalent amount of ascorbic acid in citrus fruits and tomatoes maintain a liberal level of ascorbic acid in the plasma <sup>79</sup>

There seems to be little doubt that ascorbic acid is of great importance in the healing of wounds, and during the past year further research in this direction has added greatly to present knowledge Lund and Crandon <sup>80</sup> reported on a study of 58 patients who underwent operations on the biliary tract In patients in whom the intake of ascorbic acid was poor or the level of ascorbic acid in the plasma was low preoperatively or both, hernia developed postoperatively more often than in those patients in whom the supply of ascorbic acid was good preoperatively On the experimental side of this problem Bartlett and his group <sup>81</sup> presented some interesting data These authors studied the effect of ascorbic acid on healing of wounds by making abdominal incisions on guinea pigs and removing a specimen of tissue for a control biopsy The wound was allowed to heal for a suitable period, and then the healing tissue was excised The ascorbic acid content of the excised tissues was then measured Animals on a scorbutogenic diet did not show any essential increase in ascorbic acid in the healing tissue over that in control specimens and only slightly lowered values in the remainder of the abdominal wall However,

73 Wiehl, D G, and Kantorovitz, M Medical Evaluation of Nutritional Status XI An Analysis of Sources of Errors in the Photometric Macromethod of Determining Ascorbic Acid in Plasma, *Milbank Memorial Fund Quart* **20** 178-206 (April) 1942 Harris, L J Critique of the Saturation Method for Determining Vitamin-C Levels, *Lancet* **1** 644-646 (May 30) 1942

74 Rall, E P, and Sherry, S Adult Scurvy and the Metabolism of Vitamin C, *Medicine* **20** 251-340 (Sept) 1941

75 Moise, D D Scurvy in Children, *North Carolina M J* **3** 290-295 (June) 1942

76 Cameron, D G, and Mills, E S Scurvy in Montreal, *Canad M A J* **46** 548-550 (June) 1942

77 Dann, M The Influence of Diet on the Ascorbic Acid Requirement of Premature Infants, *J Clin Investigation* **21** 139-144 (March) 1942

78 Harris, L J Vitamin-C Levels of School-Children and Students in War-Time, *Lancet* **1** 642-644 (May 30) 1942

79 Bessey, O A, and White, R L The Ascorbic Acid Requirement of Children, *J Nutrition* **23** 195-204 (Feb) 1942

80 Lund, C C, and Crandon, J H Ascorbic Acid and Human Wound Healing, *Ann Surg* **114** 776-790 (Oct) 1941

81 Bartlett, M K, Jones, C M, and Ryan, A E Vitamin C and Wound Healing I Experimental Wounds in Guinea Pigs, *New England J Med* **226** 469-473 (March 19) 1942



## BIOTIN

This relative newcomer to the field of nutrition was considered briefly in last year's review. Now, for the first time, induced biotin deficiency has been produced in human beings<sup>68</sup>. Many investigators have noticed that the inclusion of large amounts of egg white in special experimental diets will produce definite nutritional disease in animals. This disease is commonly called "egg white injury" and is characterized chiefly by the appearance of a rather severe, general eczematous dermatitis involving the eyelids and the lips. Egg white injury can be prevented or cured by administration of biotin. It is due to an induced biotin deficiency caused by the binding of dietary biotin by a protein fraction of raw egg white (avidin), thereby preventing the absorption of this vitamin from the intestinal tract<sup>69</sup>.

Sydenstricker and his associates maintained 4 volunteers on a diet poor in all vitamins of the B group (except riboflavin, supplied by egg white), at least 30 per cent of the total caloric intake was supplied by desiccated egg white. During the third and the fourth week all 4 of these subjects had a fine scaly dermatitis, which disappeared spontaneously and which did not itch. During the seventh and the eighth week all 4 patients exhibited a grayish pallor of the skin, apparently owing to peripheral vasoconstriction, and the 3 white volunteers had definite atrophy of the lingual papillae, which the Negro volunteer did not have until the fourteenth week. By the ninth and the tenth week dryness of the skin of the extremities, well defined reticulation and tendency again to fine, grainy desquamation were present in all cases. Ocular or genital lesions were not observed. After the fifth week depression, muscular pain, anorexia and precordial pain developed. All of these symptoms and signs were cured rapidly by parenteral administration of a biotin concentrate in doses representing 150 to 300 micrograms of biotin per day.

## ASCORBIC ACID

*Chemical and Physiologic Properties*—The level of ascorbic acid in the blood of human beings is not significantly affected by elevating the body temperature to 104 F for periods as long as four hours<sup>70</sup>. In the guinea pig the sedative effect of soluble pentobarbital is greatly prolonged if the animal has been kept for periods of thirty-three days on a diet deficient in ascorbic acid. This prolongation of sedative effect can promptly be brought to normal by addition of ascorbic acid to the diet. Deficiency of ascorbic acid, however, had no such effect on the metabolism of pentothal sodium<sup>71</sup>. An interesting study by Rothman<sup>72</sup> suggested that the influence of ascorbic acid on oxidation of tyrosine by ultraviolet irradiation in vitro is threefold. 1. It markedly furthers formation of dihydroxyphenylalanine

68 Sydenstricker, V. P., Singal, S. A., Briggs, A. P., DeVaughn, N. M., and Isbell, H. Observations on the "Egg White Injury" in Man, *J. A. M. A.* **118** 1199-1120 (April 4) 1942.

69 Eakin, R. E., McKinley, W. A., and Williams, R. J. Egg-White Injury in Chicks and Its Relationship to a Deficiency of Vitamin H (Biotin), *Science* **92** 224-225 (Sept. 6) 1940. Eakin, R. E., Snell, E. E., and Williams, R. J. A Constituent of Raw Egg White Capable of Inactivating Biotin in Vitro, *J. Biol. Chem.* **136** 801-802 (Dec.) 1940. Gyorgy, P., Rose, C. S., Eakin, R. E., Snell, E. E., and Williams, R. J. Egg-White Injury as the Result of Non-absorption or Inactivation of Biotin, *Science* **93** 477-478 (May 16) 1941.

70 Osborne, S. L., and Farmer, C. J. Influence of Hyperpyrexia on Ascorbic Acid Concentration in the Blood, *Proc. Soc. Exper. Biol. & Med.* **49** 575-578 (April) 1942.

71 Richards, R. K., Kueter, K., and Klatt, T. J. Effect of Vitamin C Deficiency on Action of Different Types of Barbiturates, *Proc. Soc. Exper. Biol. & Med.* **48** 403-409 (Nov.) 1941.

72 Rothman, S. In Vitro Studies on Pigmentation. II. Influence of Ascorbic Acid on Oxidation of Tyrosine by Ultraviolet Irradiation, *J. Invest. Dermat.* **5** 67-74 (April) 1942.

For many years it has been recognized that vitamin D and the irradiated sterol concentrates may produce reactions. Nausea, vomiting, anorexia, abdominal pain, diarrhea, headache and muscular weakness are the symptoms which usually accompany this reaction. Tumulty and Howard<sup>90</sup> reported 2 cases in which a preparation containing vitamin D was administered in large doses, with accompanying prolonged hypercalcemia and persistent impairment of renal function, as measured by inability to concentrate urine normally.

#### VITAMIN E

*Chemistry and Physiology*—It has been suggested<sup>91</sup> and adopted<sup>92</sup> that synthetic racemic tocopherol (tocopheryl) acetate be made the international standard for vitamin E. The international unit is the vitamin E activity of 10 mg of the standard preparation (racemic tocopherol acetate in olive oil, 10 Gm contains 10 mg of synthetic racemic tocopherol acetate). The quantity represents the average amount which prevents resorption gestation in rats deprived of vitamin E when the substance is administered orally.

A new photoelectric method for determination of alpha tocopherol in human serum was reported within the last year<sup>93</sup>.

*Clinical Application*—The hope of success of vitamin E in the treatment of various neuromuscular diseases of human beings has faded rapidly during the past year. A large number of patients with multiple sclerosis, progressive muscular atrophy, muscular dystrophy, amyotrophic lateral sclerosis and other diseases have had adequate treatment with natural and synthetic preparations of vitamin E. The results from such treatment have been most discouraging<sup>94</sup>. Whether further experimental<sup>95</sup> and clinical<sup>96</sup> trials are warranted must be left to the decision of the individual physician. Claims<sup>97</sup> have continued to be made that vitamin E is of value in treatment of fibrositis, but the subject needs further clinical investigation.

90 Tumulty, P. A., and Howard, J. E. Irradiated Ergosterol Poisoning. Report of Two Cases, *J. A. M. A.* **119** 233-236 (May 16) 1942.

91 Hume, E. M. Standardization of Vitamin E, *Nature*, London **148** 472-473 (Oct 18) 1941.

92 Memorandum on the International Standard for Vitamin E, Department of Biological Standards, National Institute for Medical Research, Hampstead, London, Bull. Health Organ., League of Nations **9** 443-446, 1940-1941.

93 Mayer, G. G., and Sobotka, H. Photoelectric Determination of *dl*- $\alpha$ -Tocopherol in Serum, *J. Biol. Chem.* **143** 695-699 (May) 1942.

94 Meller, R. L. An Evaluation of Vitamin E in the Treatment of Multiple Sclerosis and the Progressive Muscular Atrophies, *Journal-Lancet* **61** 471-478 (Dec) 1941. DeJong, R. N. Vitamin E and Alpha Tocopherol Therapy of Neuromuscular and Muscular Disorders, *Arch. Neurol. & Psychiat.* **46** 1068-1073 (Dec) 1941. Harvey, R. W., and Hume, P. B. Vitamin E and Nervous Diseases, *California & West Med* **55** 293-295 (Dec) 1941. Merwarth, H. R. Synthetic Vitamin E in the Treatment of Amyotrophic Lateral Sclerosis and Related Disorders. Report of Six Cases, *Dis. Nerv. System* **2** 325-329 (Oct) 1941. Viets, H. R., Trowbridge, E. H., Jr., and Gundersen, T. E. The Treatment of Certain Muscular Atrophies with Vitamin E, with a Note on Diagnosis and the Electromyograms, *Am. J. M. Sc.* **203** 558-556 (April) 1942. Lubin, A. J. Use of Alpha Tocopherol in the Treatment of Neuromuscular Disorders, *Arch. Int. Med.* **69** 836-855 (May) 1942. Hawke, W. A. Vitamin Therapy of Muscular Dystrophy, *Canad. M. A. J.* **47** 153-155 (Aug) 1942.

95 Blakeslee, G. A. Some New Applications of Synthetic Vitamin E Therapy, *J. Nerv. & Ment. Dis.* **96** 184-190 (Aug) 1942.

96 Jolliffe, N. Treatment of Neuropsychiatric Disorders with Vitamins, *J. A. M. A.* **117** 1496-1500 (Nov 1) 1941.

97 Ingham, D. W. The Treatment of Fibrositis and Vitamin E, *M. Ann. District of Columbia* **10** 470-471 (Dec) 1941. Steinberg, C. L. The Tocopherols (Vitamin E) in the Treatment of Primary Fibrositis, *J. Bone & Joint Surg.* **24** 411-423 (April) 1942.

when the supply of ascorbic acid was high, a striking increase in the ascorbic acid content of healing tissue over that of the control specimen of tissue was demonstrated. In addition, the tensile strength of wounds in which ascorbic acid content was high was much greater than that of those in which it was low. In studies of wounds in human beings this group of investigators<sup>82</sup> found that a sufficient depletion of ascorbic acid produces a decreased ascorbic acid content and tensile strength of healing wounds in the skin and in fascia. However, before these changes appear a fasting level of ascorbic acid of less than 0.2 mg per hundred cubic centimeters of plasma must be reached. Others<sup>83</sup> have reported that increasing the dose of ascorbic acid above the normal daily requirement does not result in greater than normal development of tensile strength in wounds and that addition of vitamin P to the diet does not improve the healing process. Deficiency of the vitamin B complex apparently has little effect in healing of wounds in rats<sup>84</sup>. As was stated in an editorial in *The Journal of the American Medical Association*,<sup>85</sup> these observations suggest that under normal conditions of intake and absorption of food the tissues of the average person contain sufficient ascorbic acid to insure normal healing of wounds. The remaining problem is that of demonstrating which person will require supplementary ascorbic acid therapy preoperatively and postoperatively.

The interesting relation of ascorbic acid to arsenical therapy in human beings has continued to receive attention. Of 38 patients who gave strongly positive reactions to patch tests with a 30 per cent solution of neoarsphenamine, only 32 had positive reactions if ascorbic acid was added to the neoarsphenamine<sup>86</sup>. Studies of the plasma levels of ascorbic acid in these patients indicated that such levels do not exert as great an effect in preventing cutaneous reactions to patch tests as the local application of ascorbic acid does. It was suggested that patch tests be performed with 30 per cent neoarsphenamine plus 10 per cent ascorbic acid and that patients who react positively to this test most likely will not be able to tolerate neoarsphenamine. Similar studies have been reported by Abt<sup>87</sup>.

#### VITAMIN D

An excellent summary of the relation of vitamin D to ossification appeared,<sup>88</sup> and a method for estimation of vitamin D in blood serum was reported<sup>89</sup>.

82 Bartlett, M. K., Jones, C. M., and Ryan, A. E. Vitamin C and Wound Healing. II. Ascorbic Acid Content and Tensile Strength of Healing Wounds in Human Beings, *New England J. Med.* **226** 474-481 (March 19) 1942.

83 Hartzell, J. B., and Stone, W. E. The Relationship of the Concentration of Ascorbic Acid of the Blood to the Tensile Strength of Wounds in Animals, *Surg., Gynec. & Obst.* **75** 1-7 (July) 1942.

84 Holden, J. C., and Crile, G., Jr. Influence of Vitamin B Complex Deficiency and Partial Starvation on Wound Healing. Experimental Research with Rats, *Arch. Surg.* **44** 1106-1110 (June) 1942.

85 Vitamin C and Wound Healing, editorial, *J. A. M. A.* **119** 564-565 (June 13) 1942.

86 Bundeson, H. N., Aron, H. C. S., Greenebaum, R. S., Farmer, C. J., and Abt, A. F. The Detoxifying Action of Vitamin C (Ascorbic Acid) in Arsenical Therapy. I. Ascorbic Acid as a Preventive of Reactions of Human Skin to Neoarsphenamine, *J. A. M. A.* **117** 1692-1695 (Nov. 15) 1941.

87 Abt, A. F. The Human Skin as an Indicator of the Detoxifying Action of Vitamin C (Ascorbic Acid) in Reactions Due to Arsenicals Used in Antisymphilitic Therapy, *U. S. Nav. M. Bull.* **40** 291-303 (April) 1942.

88 McGowan, J. P. On Ossification and Vitamin D Action, *Edinburgh M. J.* **49** 190-199 (March) 1942.

89 Warkany, J., Guest, G. M., and Grabill, F. J. Estimation of Vitamin D in Blood Serum. Vitamin D in Human Serum During and After Periods of Ingestion of Large Doses of Vitamin D, *J. Lab. & Clin. Med.* **27** 557-565 (Jan.) 1942.

*Clinical Use*—Previous reports showing the value of vitamin K in preventing hemorrhage associated with deficiency of prothrombin in the circulating blood continue to be confirmed. A few new and interesting clinical developments have been reported. Rhoads and Fitz-Hugh<sup>107</sup> studied the case of a white youth aged 18 who had had episodes of hemorrhagic diathesis throughout most of his life. This diathesis was due apparently to an idiopathic hypoprothrombinemia and an associated abnormality of the fibrinogen. Rhoads and Fitz-Hugh were unable to correct the deficiency of prothrombin by administration of synthetic substances with vitamin K activity. Another interesting case of hypoprothrombinemia was reported by Coller and Fairis<sup>108</sup>. Within three days after a massive gastric hemorrhage the patient received 3,200 cc of blood and, in addition, 7,500 cc of fluid intravenously. Two days later a marked deficiency of prothrombin was found which was nearly completely corrected within twenty-four hours by administration of vitamin K. The patient had taken a normal diet and did not have any abnormality of the biliary tract or the liver. At necropsy a bleeding gastric ulcer was found. The authors suggested that sufficient depletion of prothrombin reserve could result from repeated dilution of the blood with solutions of sodium chloride and dextrose. This possibility deserves further investigation. These authors also confirmed the observation that deficiency of prothrombin can develop after simple, continued aspiration of bile from the gastrointestinal tract with suction apparatus<sup>109</sup>.

In contrast to previous reports, Levy<sup>110</sup> observed that 32 per cent of the patients with pulmonary tuberculosis studied by him had a more or less marked degree of prothrombin deficiency. It is interesting that 87 per cent of these patients had parenchymal hepatic damage. Levy also found that vitamin K had a beneficial effect on the treatment and prevention of hemorrhage in tuberculosis.

Vitamin K continues to be widely and successfully employed in treatment and prevention of certain hemorrhagic diseases of newborn infants. Hellman and Shettles<sup>111</sup> have advocated that 2 mg of menadione, or any preparation with similar activity, be given to pregnant women daily for at least two weeks prior to onset of labor. They stated that 20 to 40 per cent of the 128,000 infants who do not survive each year show some evidence of cerebral hemorrhage. It is hoped that the plan they suggested may result in the saving of many of these lives.

Ross and Malloy<sup>112</sup> reported on a group of newborn infants suffering from asphyxia who had a marked deficiency of prothrombin and suggested that anoxemia may be a factor in production of deficiency of prothrombin. Induced anoxemia in newborn chicks resulted in similar findings. The observations are supported by the experimental work of Tocantins, mentioned previously<sup>103</sup>.

107 Rhoads, J. E., and Fitz-Hugh, T., Jr. Idiopathic Hypoprothrombinemia—An Apparently Unrecorded Condition, *Am J M Sc* **202** 662-670 (Nov.) 1941.

108 Coller, F. A., and Fairis, J. M. The Management of the Jaundiced Patient, with Special Reference to Vitamin K, *Surg, Gynec & Obst* **73** 21-29 (July) 1941.

109 Butt, H. R., and Snell, A. M. Vitamin K, Philadelphia, W. B. Saunders Company, 1941.

110 Levy, S. Vitamin K in Tuberculosis, with Special Reference to Pulmonary Hemorrhage, *Am Rev Tuberc* **45** 377-391 (April) 1942.

111 Hellman, L. M., and Shettles, L. B. The Prophylactic Use of Vitamin K in Obstetrics, *South M J* **35** 289-293 (March) 1942.

112 Ross, S. C., and Malloy, H. T. Blood Prothrombin in the New-Born. The Effect of Vitamin K upon the Blood Prothrombin and upon Haemorrhagic Disease of the New-Born, *Canad M A J* **45** 417-421 (Nov.) 1941.

## VITAMIN K

*Physiology and Chemistry*—This year little can be added to the excellent consideration of the chemistry of vitamin K by Fieser,<sup>98</sup> mentioned in last year's review. New calorimetric procedures for accurate chemical determinations of K vitamins have been described,<sup>99</sup> and they give hope that even simpler quantitative procedures soon will be available. Scudi<sup>100</sup> reported the interesting observation that when menadione is added to whole unclotted blood, it causes marked formation of methemoglobin and that the drug is converted rapidly to some other substance. However, under comparable conditions vitamin K<sub>1</sub> does not produce methemoglobin.

An excellent summary of the role of vitamin K in coagulation of blood appeared,<sup>101</sup> and Rhoads and his group<sup>102</sup> reviewed the work on experimental hypoprothrombinemia. Tocantins<sup>103</sup> reported that exposure of citrated or oxalated plasma to an air current is followed by rapid diminution in its prothrombin activity. This phenomenon is corrected by addition of carbon dioxide but is not affected by addition of oxygen. The author suggested that asphyxia or hyperventilation may lead to significant fluctuation in the level of prothrombin in the blood.

While attempting to produce experimental hemorrhagic disease in newborn animals Moore and his associates<sup>104</sup> observed that rabbits which received a diet deficient in vitamin K for forty days and then mated invariably aborted from the tenth to the fourteenth day of pregnancy. Necropsy revealed retroplacental hemorrhage. It is interesting that the level of prothrombin in the plasma did not fall to so-called "critical levels" and that the only point of hemorrhage was in the placenta. It is suggested that the placenta is unusually susceptible to deprivation of vitamin K.

The possibility that pancreatic disease also may be accompanied by deficiency of prothrombin is suggested by the report that pancreatic achylia and pancreatectomy, at least in the cat, are followed by reduction in the level of prothrombin in the blood.<sup>105</sup>

Another interesting contribution on the physiology of vitamin K was made by Overman and his associates.<sup>106</sup> These authors observed that when the rat ingests 3,3'-methylenebis-(4-hydroxycoumarin) need for vitamin K appears to be increased. Vitamin K was found to counteract hypoprothrombinemia induced by the anticoagulant whether given before the anticoagulant, with it or twelve hours later.

98 Fieser, L. F. The Chemistry of Vitamin K, *Ann Int Med* **15** 648-658 (Oct) 1941.

99 Scudi, J. V., and Buhs, R. P. A Colorimetric Oxidation-Reduction Method for the Determination of the K Vitamins, *J Biol Chem* **141** 451-464 (Nov) 1941. Irreverre, F., and Sullivan, M. X. A Colorimetric Test for Vitamin K<sub>1</sub>, *Science* **94** 497-498 (Nov 21) 1941.

100 Scudi, J. V. Reactions of 2-Methyl-1,4-Naphthoquinone (Menadione) with Whole Blood and Plasma in Vitro, *Proc Soc Exper Biol & Med* **50** 16-17 (May) 1942.

101 D'Alessandro, A. J. Vitamin K and Its Role in Blood Coagulation, *Am J Surg* **57** 104-111 (July) 1942.

102 Rhoads, J. E., Warren, R., and Panzer, L. M. Experimental Hypoprothrombinemia, *Am J M Sc* **202** 847-861 (Dec) 1941.

103 Tocantins, L. M. Loss of Prothrombin Activity in Plasma Exposed to Air Current, *Proc Soc Exper Biol & Med* **49** 251-253 (Feb) 1942.

104 Moore, R. A., Bittenger, I., Miller, M. L., and Hellman, L. M. Abortion in Rabbits Fed a Vitamin K Deficient Diet, *Am J Obst & Gynec* **43** 1007-1012 (June) 1942.

105 Sproul, E. E., and Sanders, E. K. Effect of Pancreatic Achylia on Vitamin K Absorption and Prothrombin Time, *Am J Physiol* **135** 137-148 (Dec 1) 1941.

106 Overman, R. S., Field, J. B., Baumann, C. A., and Link, K. P. Studies on the Hemorrhagic Sweet Clover Disease. IX. The Effect of Diet and Vitamin K on the Hypoprothrombinemia Induced by 3,3'-Methylenebis (4-Hydroxycoumarin) in the Rat, *J Nutrition* **23** 589-602 (June) 1942.

## Book Reviews

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**Intestinal Obstructions A Physiological and Clinical Consideration with Emphasis on Therapy, Including Description of Operative Procedures** By O H Wangenstein Second edition Price, \$7 Pp 484 Springfield, Ill Charles C Thomas, Publisher, 1942

This is an excellent treatise on the important and serious clinical problem of intestinal obstruction From the preface through the last page of the last chapter, which deals with obstructions owing to vascular causes, the book is full of practical suggestions regarding the manner in which intestinal obstruction disturbs the economy of the body and regarding diagnostic, as well as therapeutic, procedures for this most devastating human ailment

The author wisely has divided the subject into four parts as follows physiologic and clinical considerations, general diagnosis, therapeutic considerations, and special obstructions

Part 1, on physiologic and clinical considerations of intestinal obstruction, consists of one chapter of 60 pages which is divided into seven parts In this portion of the book the author deals with the systemic effects, character and source of distention and its manifestations on the intestinal wall Absorption in the presence of obstruction, the significance of the factor of loss of blood in strangulating obstructions and the nature of the toxemia associated with obstruction are explained

Although it is stated that no direct and unequivocal answer has been obtained to the question of lethal factors in obstruction, the author's opinion seems to be that apart from the loss of fluids and electrolytes, which is of serious consequence, the chief effects of obstruction are mechanical and concern intraenteric pressure as related to absorption and the viability of the intestinal wall When the viability of the wall has become impaired, then permeation by bacteria and other deadly agents occurs, but this is a secondary rather than a primary phenomenon

Part 2, on general diagnostic considerations, is 41 pages long and is divided into two chapters, in one diagnostic methods for acute abdominal disorders and in the other the recognition of obstruction are considered In the latter chapter the author explains the methods of determining that obstruction exists, of localizing the obstructing lesion and of determining whether obstruction is partial or complete and finally the mechanism of the obstruction

In part 3 seven chapters (chapters 4 to 10 inclusive), 140 pages, are devoted to the management of acute intestinal obstruction In chapter 4 the author considers guiding principles in the treatment of acute abdominal lesions, in chapter 5 the important supportive measures are listed, namely, administration of physiologic solution of sodium chloride, transfusion of blood and plasma and inhalation of oxygen in high concentrations, and in chapter 6 the technic of decompression by application of suction through duodenal tubes is outlined Indications for this conservative method of treatment and shortcomings of suction are explained In chapter 7 operative procedures, preoperative preparation and choice of anesthetic are outlined Chapter 8 is devoted to closed aseptic resection Postoperative treatment is considered in chapter 9 and mortality in chapter 10

In part 4, on the special obstructions, fifteen chapters are devoted to a discussion of obstruction due to congenital atresia of the intestine, the imperforate anus, tumors and strictures of the intestinal wall, obturation, fecal obstruction, as occurs in megacolon, compression of the bowel by extrinsic conditions, such as pelvic lesions, adhesions and bands, external hernia, internal hernia, volvulus, intussusception, errors in development of the intestine, inhibition (paralytic) ileus, spastic ileus, and obstruction owing to vascular causes

Any practitioner of medicine will be proud to have this book in his reference library Every teacher of medicine should have it available as a textbook, for it contains the most modern information on the subject and sound information for students More than that, any one reading it will find that it is written in an interesting, almost fascinating manner

**Publicaciones del centro de investigaciones fisiologicas** Vol 5 Pp 388, with 28 illustrations Buenos Aires Pabellon "Las Provincias," Hospital Torno, 1941

This collection of eleven papers from the Center of Tuberculosis Research, Buenos Aires, Argentina, under the direction of Prof Roque A Izzo, testifies to the thoroughly scientific work being carried on in Argentina, as in other South American countries The influence of the best in German and in French medical thought on this subject is obvious North American authors are also frequently cited The summaries in German, French and English will aid the reader who is not familiar with Spanish, in which language the text is written

The percutaneous use of vitamin K has again been advocated,<sup>113</sup> but other investigators<sup>114</sup> have found this method of administration unsatisfactory because of the ensuing dermatitis in more than 50 per cent of the cases studied

Seligman and his associates<sup>115</sup> have described a method of preparing pure vitamin K in colloidal suspension for intravenous administration. A single 10 mg dose of this compound has a much longer effect than that of an equivalent dose of menadione. This compound administered in this dose to a patient with an elevated prothrombin time resulted in a normal prothrombin time for twenty-six days.

The old problem of attempting to evaluate the degree of hepatic damage by the response of prothrombin to administration of vitamin K has received considerable attention. Kark and Souter,<sup>116</sup> in an effort to interpret better this test of hepatic function, have subdivided the response of prothrombin to vitamin K into five subdivisions. In the first group the response to vitamin K is prompt, and it was assumed that in these instances no gross hepatic damage exists. In the second group the level of prothrombin in the blood rises somewhat but remains fixed at a subnormal level despite treatment with vitamin K; in this group the hepatic damage is of a moderate and variable degree. In the third group the level of prothrombin in the blood gradually rises as clinical improvement becomes apparent. In the fourth group the level of prothrombin fluctuates in a subnormal zone which is above the threshold for hemorrhage, irrespective of therapy. Patients in this group have chronic hepatic disease of long standing, usually unassociated with jaundice. In the fifth group the level of prothrombin decreases in spite of therapy or remains below the level for hemorrhage. In this group hepatic damage is severe and widespread.

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113 Fantl, P, and Corkill, A. B. Percutaneous Treatment of Vitamin K Deficiency, *M. J. Australia* **2** 540-541 (Nov 8) 1941

114 Page, R. C, and Bercovitz, Z. Dermatitis from Topical Application of 2-Methyl-1,4-Naphthoquinone (Synthetic Vitamin K Analogue), *Am. J. M. Sc.* **203** 566-569 (April) 1942

115 Seligman, A. M., Hurwitz, A., Frank, H. A., and Davis, W. A. The Intravenous Use of Synthetic Vitamin K, *Surg., Gynec. & Obst.* **73** 686-701 (Nov.) 1941

116 Kark, R., and Souter, A. W. The Response to Vitamin K. A Liver-Function Test, *Lancet* **2** 693-696 (Dec 6) 1941

The chapter by Snell on the physiologic considerations of the problems arising in patients with gastric carcinoma is excellent. Of especial interest is the portion of the chapter dealing with vitamin-deficient states observed in these patients.

The chapter by MacCarthy on surgical pathology is likewise of interest, and the discussion of the metastatic spread of gastric carcinoma is well carried out. Desjardins presents an excellent discussion of the problems and procedures involved in the roentgen treatment of gastric carcinoma.

**Autonomic Regulations** By Ernst Gellhorn, M.D. Price, \$5.50 Pp 373, with 80 illustrations New York Interscience Publishers, Inc., 1943

This is a highly technical book which sums up a large amount of research on the way in which autonomic centers, particularly in the hypothalamic region, affect many of the automatic functions of the body. Much of the work has been done by Dr. Gellhorn, but he also cites one thousand, one hundred papers by investigators in this field. Subjects discussed are adjustment reactions to changes in the carbon dioxide content of the blood and to anoxia, asphyxia, hemorrhage and hypoglycemia. There are chapters on the autonomic regulation of the cerebral circulation, on the hormones of the hypophysis and on the sympathico-adrenal and the vaso-insulin systems. There are chapters on the roles of the sympathetic, parasympathetic and somatic nervous systems in regulating several of the involuntary functions of the body. Chapter 13 is on reflexes from the carotid sinus, chapter 14 discusses the autonomic basis of emotion, chapter 18 is on the adjustment reactions during general and spinal anesthesia, and chapter 19 deals with what has been learned about changes in the behavior of the autonomic nervous system in patients suffering from schizophrenia.

The book will be of particular value to the student who wishes to find out how the sympathetic and parasympathetic systems of nerves are behaving during a number of situations when the body is under severe strain.

**Manual of Oxygen Therapy Techniques** By Albert H. Andrews Jr. Pp 181, with 16 tables and 33 figures Chicago The Year Book Publishers, Inc., 1943

This handy little manual takes up in minutest detail all technical matters of oxygen therapy including the use of carbon dioxide, helium and water vapor. There are diagrams and photographs of oxygen tents, face masks and other apparatus and exact instructions for the care and use of all this equipment. The book should be useful to every one but especially to house officers and nurses.

**Chronic Pulmonary Disease in South Wales Coalminers** I Medical Studies Report by the Committee on Industrial Pulmonary Disease Medical Survey, by P. D'Arcy Hart and E. A. Aslett, with contributions by D. Hicks and R. Yates Pathological Report by T. H. Belt, with assistance from A. A. Ferris Price, 10s, 6d Pp 222 London His Majesty's Stationery Office, 1942

This report on the occurrence and nature of pneumoconiosis in coal miners is the result of a study begun in 1937 and carried through despite the exigencies of war. Its appearance at this time can be credited to the British quality of seeing a job through, while its tremendous thoroughness and its scientific caution in drawing conclusions must be credited to the able collaborators who made and wrote up the medical survey and the pathologic report. The incidence of pneumoconiosis is studied in relation to mining conditions, the type of coal mined, the kind and the duration of work done, the incidence of tuberculous infection and the degree of disability. A prenodular stage of reticulation is described both roentgenologically and pathologically. The illustrations of roentgen changes, showing both whole chests and detailed enlargements of limited areas, are extraordinarily good. There is an excellent bibliography. In addition to those persons with a special interest in silicosis, physicians and roentgenologists in all coal mining regions will find in this report a rich seam well worth digging.

**Medical Progress** Edited by Robert N. Nye Price, \$5 Pp 675 Springfield, Ill Charles C Thomas, Publisher, 1942

Every one who looks through current journals must be impressed with the value of the review articles which appear in the *New England Journal of Medicine*. It is extremely convenient, therefore, to find under one cover the entire series of articles for 1941. It is not possible to review the material in detail, but the authoritative character of the articles is illustrated by such names as Fulton, on aviation medicine, Weiss, on arteritis, Janeway, on bacteriologic matters, Joslin, on diabetes, and Aub, on endocrine glands. The makeup of this book of 675 pages is attractive, and there is an index.



The detailed analysis of the results of artificial pneumothorax treatment is one of the best to be found in the world's literature Prof Oscar P Aguilar's discussion of Ranke's secondary tuberculosis is thorough and stimulating The shorter papers on results of the Jacobaeus operation, absorption of ultraviolet light, behavior of lymphocytes to tubercle bacilli in vitro and tuberculin allergy of infants are all of the same high standard

**The Care of the Aged (Geriatrics)** By Malford W Thewlis, M D Fourth edition, revised Price, \$7, cloth Pp 589, with 50 illustrations St Louis C V Mosby Co, 1942

The disproportionate increase in population in the higher age groups in this country in the past twenty years, which in all likelihood will increase still further, has stimulated much interest in the subject of gerontology and geriatrics by physiologists, pathologists and clinicians

This work is balanced poorly, mainly because certain features are emphasized unduly, while others are neglected or merely mentioned, furthermore, there is too much repetition There is a moderately comprehensive bibliography at the end of each chapter

The reviewer feels that this work falls too far short of its possibilities to encourage students or clinicians to invest in it

**Synopsis of Pathology** By W A D Anderson, M D, Assistant Professor of Pathology, St Louis University School of Medicine, Pathologist, St Mary's Group of Hospitals Price, \$6, cloth, octavo Pp 638, with 294 illustrations in the text and 17 colored plates St Louis C V Mosby Company, 1942

The author states that his purpose in compiling this book was "to fill a gap which has existed between the very elementary manuals of pathology and the abundant excellent larger textbooks and reference works" It is the opinion of the reviewer that he has succeeded in large measure in producing "a concise synopsis of pathology in which essentials are included but the broad outlines and patterns of disease are not obscured by a mass of detail"

The illustrations are well chosen and clearly reproduced A short bibliography is appended to each chapter, and a general index is included This book should be useful for quick reference by medical and by dental students as well as by clinicians in general practice

**The Food You Eat** By Samuel and Violette Classtone Price, \$2.25 Pp 277, with 18 illustrations Norman, Okla The University of Oklahoma Press, 1942

This is the best semipopular book on food and nutrition the reviewer has yet seen The writers are obviously experts and have a large backlog of solid scientific information to draw on They write well and make their points with a quiet emphasis which is sufficiently convincing The flamboyant or evangelistic style used by so many propagandists of nutrition is conspicuously absent The theoretic part of the subject is covered in such a way as to be intelligible to the average educated reader, and the practical discussion of food and of menus is satisfactory The book does credit to the university press which produced it

**Carcinoma of the Stomach** By Waltman Walters, M D, Howard K Gray, M D, James T Priestley, M D, and associates in the Mayo Clinic and the Mayo Foundation Price, \$8.50 Pp 576, with 178 illustrations on 143 figures, 2 in colors Philadelphia W B Saunders Company, 1942

The chief new contribution of this monograph is a statistical analysis of almost 11,000 cases of gastric carcinoma observed at the Mayo Clinic from 1907 to 1938 While this material is of inestimable value, it could well have been presented in a volume much reduced in length

Most valuable is the section (the last two chapters and the appendix) by Dr Joseph Berkson containing the biometric analysis of the data The reviewer was impressed with the fact that in the 10,890 cases studied, 99 per cent of the patients who survived were traced over a five year period and 98 per cent of the patients who survived were traced over a twenty year period The correction of the data for the normal survival rate of the population at large makes the interpretation of the results of the observation of the population sample represented in the study much more accurate

Of the 10,890 cases studied, the carcinomas in 43 per cent were considered to be inoperable In the remaining 57 per cent the patients were subjected to surgical procedures as follows Palliative procedures were instituted in 10 per cent, exploratory laparotomies only were done in 22 per cent, and resection was done in the remaining 25 per cent The calculated mean survival rate for the group was two and two-tenths years Twenty pages devoted to the mechanics of operating room technic and enumeration of the duties of the operating room nurses before and after their breakfast might well have been omitted The 50 pages devoted to anesthesia might have been more properly included in some other textbook

## STREPTOCOCCIC AND PNEUMOCOCCIC INFECTIONS OF THE NOSE AND THROAT IN YOUNG ADULTS

INCIDENCE, EPIDEMIOLOGY AND CLINICAL FEATURES

PAUL S RHOADS, M D  
AND  
MELVIN E AFREMOW, M D  
CHICAGO

We have been impressed by the lack of detailed and accurate information in medical textbooks about the most common diseases which the average American physician is called on to treat. For this reason, an attempt has been made to gather together some of the observations made in our own work on tonsillitis, pharyngitis, laryngitis and paranasal sinusitis.

It is appreciated that the clinical conditions mentioned here seldom occur alone. They are most often a part of a diffuse involvement of the upper respiratory passages. Often they are complications of other diseases. An attempt has been made, however, to separate them from ordinary uncomplicated colds, influenza, bronchitis and pneumonia. Scarlet fever enters into the discussion as a part of the hemolytic streptococcus infections of the nose and throat. Diphtheria, Vincent's angina and syphilitic infections are not considered here.

### INCIDENCE

In a nursing population averaging 1,034, over a five year period, the average monthly number requiring rest in bed because of these diseases was 27.21—approximately 2.6 per cent of the entire group. The peak was in January, February, March and April—averaging 4 to 5 per cent—with a moderate drop in May and a sharp drop in June, July and August to about 1 per cent (chart 1). In the fall months the number gradually rose, but not to the level of January and the early spring months. It is interesting to note how closely this curve parallels that of the finding of hemolytic streptococci in 1,115 cultures of material taken at all seasons of the year from the throats of our own patients who presented all types of respiratory infections (chart 2).

Also of interest is the fact that simple rhinitis and acute diffuse respiratory infections, such as influenza and grip, rose sharply during the fall months and outstripped sore throat and sinusitis in December, then fell below these during the remainder of the year. The total monthly incidence of *incapacitating* infections of the upper respiratory passages exclusive of pneumonia averaged 4 per cent for the year. While this figure may be unusually high because of the frequent exposures of this particular group of young adults, it indicates the enormous number of respiratory infections in this country. In children the incidence is probably even higher.

From the departments of medicine of Northwestern University Medical School and Illinois University Medical School

**Shock Its Dynamics, Occurrence and Management** By Virgil H. Moon, Professor of Pathology, Jefferson Medical College, Philadelphia Price, \$4.50, cloth Pp 324, with 36 illustrations Philadelphia Lea & Febiger, 1942

The subject material presented in this book is a continuation of and somewhat dependent on the material presented in a previous book by the author (*Shock and Related Capillary Phenomena*, New York, Oxford University Press, 1938)

The book is divided into two parts. The first part deals with the vascular dynamics of shock, while the second part discusses the prevention, recognition and management of shock. There is a pertinent summary at the conclusion of each chapter. The book contains an adequate number of suitable illustrations. The list of references appended cites many of the important contributions to the subject but is incomplete. The type and the format are excellent and make for easy reading.

The author shows a broader knowledge of the subject in this volume than in his first book and exhibits less bias for one particular theory of the cause of shock. The book is well written. The material included in it is presented in a satisfactory manner but is lacking as a comprehensive discussion of the subject. In view of the fact that the book is apparently not intended as a presentation of the subject in a complete manner, the discussion of terminal pneumonia, extrarenal uremia, status lymphaticus and similar subjects would appear to be of questionable value. On the whole, the book is a worthy contribution to the subject.

**A Short History of Cardiology** By James B. Herrick, M.D., Emeritus Professor of Medicine, Rush Medical College Price, \$3.50 Pp XVI + 258, with 48 illustrations Springfield, Ill. Charles C. Thomas, Publisher, 1942

Dr. Herrick is a rare person, able on passing his eightieth birthday to be regarded by his friends (and they include almost all members of the medical profession) as a man not 80 years old but 80 years young still young enough to speak and write picturesquely and even to indulge in such a youthful misdemeanor as an attack of acute appendicitis. During his medical career he has stored away a vast fund of medical lore, and in this volume he describes his own concept of the essential history of cardiology during the last three centuries.

Such a book, coming from a man of Dr. Herrick's skill as a medical author and his direct way of looking at things, is bound to be significant. He expresses himself with characteristic style, kindly, gaily, wittily and always in a clear and scholarly manner. The size and the shape of the volume are attractive. It can be slipped into one's pocket readily to be enjoyed in trains or on holidays in the country or at odd moments when medical history seems most easily perused. The illustrations make up an important feature of the publication. The original drawings or photographs from which the cuts were made have been borrowed for the occasion from the collections of certain of Dr. Herrick's cardiologic intimates, who must be pleased to have their treasures exhibited so handsomely.

Now any disciple of Aesculapius can go on a personally conducted tour through the history of heart disease with Dr. Herrick as guide. The trip is worth taking. It is a privilege to be introduced to worthies like Heberden, Parry, Stokes and the rest of the long line of equally distinguished cardiologists by a person who seems to know them all so affectionately and who indeed, is himself an important member of their brotherhood.

conditions not associated with hemolytic streptococci was 14 days. Hemolytic streptococci were responsible for about two thirds of the cases of sore throat and sinusitis.

In comparing the sore throat groups with a series of patients with scarlet fever who were of the same age and studied at the same time as those with sore throat (table 1) it was seen that cases of sore throat caused by hemolytic streptococci were complicated more than twice as frequently as cases of sore throat not caused by hemolytic streptococci, and almost exactly as frequently as the cases of scarlet fever. Numerically, the complications were quite similar, but the complications of the cases of scarlet fever were more severe, including two deaths, and renal involvement appeared more frequently.

Though full cognizance is taken of the fact that scarlet fever is a more serious disease than hemolytic streptococcus sore throat without a rash, insistence on strict quarantining of patients with scarlet fever for twenty-eight days and disregard

TABLE 1—Comparison of Complications in Three Groups of Nurses with Sore Throat

Sore Throat Caused by Hemolytic Streptococci (159 in Group)	Per cent—Cases age	Sore Throat Not Associated with Hemolytic Streptococci (81 in Group)	Per cent—Cases age	Scarlet Fever (60 in Group)	Per cent—Cases age
Sinusitis	43 27.0	Sinusitis	5 6.2	Sinusitis	6 10.0
Cervical adenitis	13 8.2	Cervical adenitis	2	Cervical adenitis (1 deep cervical abscess)	5 8.3
Otitis media	6 3.8	Otitis media	1	Otitis media	4 6.7
Rheumatic fever	5	Rheumatic fever	1	Rheumatic fever	1
Persistent tachycardia	2	Persistent tachycardia	1	Acute polyarthrititis	2
Reactivation of rheumatic fever	1	Persistent pharyngitis and tonsillitis	2	Persistent tachycardia	1
Rheumatoid arthritis	1	Persistent asthenia	1	Acute nephritis (1 death)	3 5.0
Persistent tonsillitis and pharyngitis	4 2.5	Bronchitis	2	Transient albuminuria	6 10.0
Acute nephritis	1	Peritonsillar abscess	1	Hemolytic streptococcus septicemia (death)	1
Persistent asthenia	2	Lumbar myositis	1	Pyelitis	1
Peritonsillar abscess	1	Total	17 21.0	Acute enteritis	1
Erysipelas	1			Acute appendicitis	1
Pleuritis	1			Bronchitis	1
Lacrimal abscess	1			Total	33 55.0
Appendicitis or mesenteric lymphadenitis	1				
Hemolytic streptococcus carrier	1				
Total	84 52.8				

of quarantine for patients with sore throat without a rash still seem somewhat inconsistent.

#### NORMAL BACTERIAL FLORA OF THE THROAT AND NOSE

The extremely difficult problem of establishing what bacteria are found in the throat and nose under normal conditions must be solved before one can impute pathologic significance to certain organisms in a culture containing a number of varieties. No claim to completeness is made for our studies. Young adults who were on duty and supposedly not ill were chosen as subjects. It was often found that some of them had slight fever and slight leukocytosis. Examinations of the noses and throats of these often revealed considerable inflammation. The examinations of the total group were scattered through the months of November, January, February, March, April, May and June. For that reason the incidence of hemolytic streptococci may be a little higher than average. A typical cross section of the entire population would require a much larger series.

The smears of material from the throats (table 2) were stained with dilute gentian violet, so that Vincent's organisms could be more easily distinguished. Thus the bacteria are divided only according to their morphologic character, not according to their staining properties. The well known fact that spirilli and fusi-

DISABILITY CAUSED BY THE AVERAGE ATTACK OF SORE THROAT OR SINUSITIS

In a previous report<sup>1</sup> we showed that the average total time lost by a Cook County Hospital nurse is 75·7 days in a three year period of training—approximately 7 per cent of her total time—20·46 days of which (27 per cent) is from the afore-

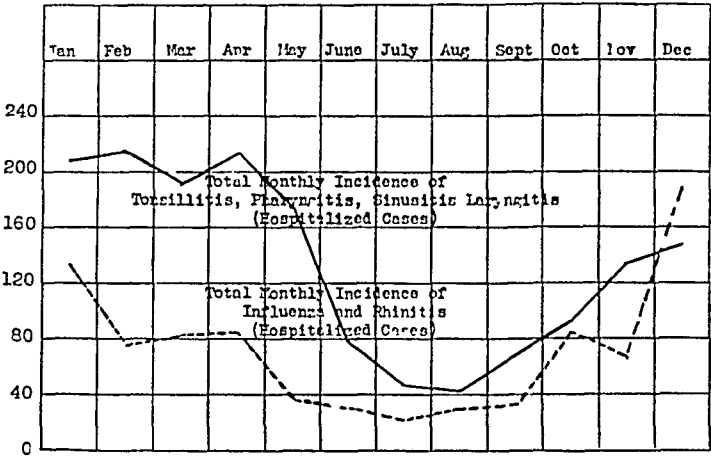


Chart 1—Incidence of respiratory infections in a nursing group averaging 1,034 members over a five year period. The number off duty with tonsillitis, pharyngitis, laryngitis and sinusitis averaged 27·21 per month—2·6 per cent of the nursing population. The number off duty with influenza, grip and simple rhinitis averaged 14·53 per month—1·4 per cent of the nursing population.

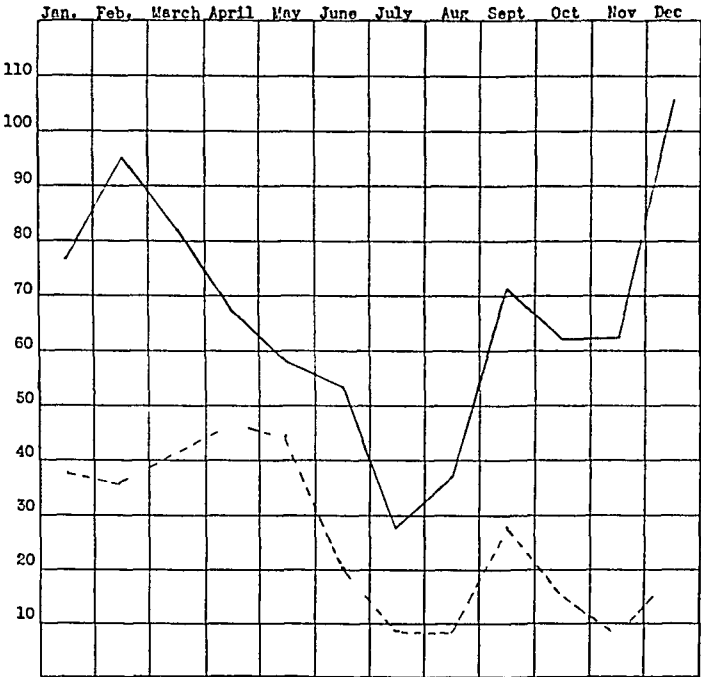


Chart 2—Monthly distribution of 1,115 cultures of material taken from the throats of persons with infections of the upper respiratory tract or exposed to such infections between Jan 1, 1937 and Jan 1, 1940. The number of cultures negative for hemolytic streptococci (—) was 800, the number positive for these organisms (---) was 315.

mentioned diseases. The average time lost per attack of sore throat and sinusitis caused by hemolytic streptococci was 16·85 days, and the time lost because of such

<sup>1</sup> Rhoads, P. S., and Afremow, M. L. Clinical and Statistical Study of Sore Throat in Young Adults, Arch. Path. 26:403 (July) 1938.

Cultures of material from the noses (table 5) were made in exactly the same way, the swab being introduced at least 1 inch (2.5 cm) into each nostril. Staphylococci were found in every culture. No special pathologic significance of the hemolytic forms appeared in this series, although it is our belief that the hemolytic *Staphylococcus aureus* in rare instances causes sinus infections and sore throat. No influenza bacilli were encountered, although they were occasionally present in cultures from persons with "diffuse upper respiratory infection."

TABLE 4—*Clinical Data on Carriers of Hemolytic Streptococci Among Eighty-Five Supposedly Normal Young Adults*

Kind of Growth	Temperature, F	White Blood Cell Count	Clinical Findings
3+	98.6	8,600	Exposed to scarlet fever two days previously, sore throat for two days
3+	98.6	8,200	Exposed to scarlet fever two days previously, throat acutely inflamed, chronic sinusitis
4+	98.6	No count	Exposed to scarlet fever two days previously, no pathologic condition found
4+	99.4	6,900	Had scarlet fever one month ago, throat still inflamed
2+	98.2	10,650	Inflamed tonsil, pains in joints
2+	99.8	13,200	Throat and nose inflamed
2+	98.6	9,000	Acute sore throat six weeks ago, pharynx still inflamed, chronic sinusitis
2+	99.2	10,800	Chronic sinusitis, continued pains in joints, throat inflamed
1+	98.0	5,100	Tonsillectomy because of arthritis three months ago, none at present
1+	98.6	10,300	Cold three weeks ago, throat still slightly inflamed, albuminuria
1+	99.4	No count	Chronic sinusitis, throat and nose inflamed
1 Col	97.6	7,800	No pathologic condition
1 Col	98.0	11,100	No pathologic condition
3 Col	98.0	10,000	Severe sore throat three months previously, throat still slightly inflamed
5 Col	99.2	10,550	Throat slightly inflamed, has a cold
2 Col	98.4	6,200	No pathologic condition
7 Col	98.6	6,300	No pathologic condition, recent exposure to scarlet fever

TABLE 5—*Analysis of Findings in Cultures of Material Taken from Noses of Young Adults Who Were Supposedly Not Ill (Chiefly Medical Students, Nurses and Hospital Technicians)\**

Organisms Noted in Cultures on Blood Agar (75 Had 1 Growth)	Times Found	Percentage
Staphylococci	75	100
Albus	58 times	
Albus haemolyticus	19 times	
Aureus	10 times	
Aureus haemolyticus	5 times	
Citreus	1 time	
Diphtheroids	10	13
Hemolytic streptococci	4	5
Anhemolytic streptococci	4	5
Green-forming cocci	5	7
Gram-positive bacilli (not further differentiated)	2	3
Gram-negative diplococci (not further differentiated)	2	3

\* All were questioned regarding recent respiratory infections and recent exposures to respiratory infections. Temperatures were taken and leukocyte counts made for most of them.

The clinical findings in those members of the series harboring hemolytic streptococci, anhemolytic streptococci and green-forming cocci in their noses are given in table 6. No heavy growth of hemolytic streptococci was found. Of the 4 persons in whose cultures they were present, 2 appeared to have normal mucous membranes. One of these, however, had been exposed to scarlet fever two days previously. The other 2 had inflammation of the nose or pharynx. Anhemolytic streptococci and green-forming cocci appeared to be unassociated with pathologic conditions in only 3 of 9 cultures. It is our belief that the organisms of the groups just mentioned rarely occur in the noses of normal persons.

form bacilli appear in a high percentage of throats and that a diagnosis of Vincent's angina can be supported only by the finding of large numbers of these organisms is again demonstrated

The cultures of material from the throats (table 3) were made by rubbing a cotton swab over the pharynx and tonsils, or tonsillar fossae, then transferring the inoculum to a blood agar plate ( $p_H$  7.4), where it was spread over the surface by a wire spreader on bent glass rod. They were read at twenty-four hours. It is seen that cocci causing greening on blood agar were found in every culture. These were known to be *Streptococcus viridans* and pneumococci, but no differentiation was attempted in this series. They are mentioned because it seems still not to

TABLE 2—*Analysis of Findings in Smears of Material Taken from Throats of Young Adults Who Were Supposedly Not Ill (Chiefly Medical Students, Nurses and Hospital Technicians)*\*

Organisms Noted in 78 Smears Made †	Times Found	Percentage
Cocci (no differentiation attempted)	77	99
Bacilli not with the morphologic character of fusiform bacilli (no further differentiation)	61	78
Fusiform bacilli	22	28
Spirilli	10	13
Mycelia	5	6

\* All were questioned regarding recent respiratory infections and recent exposures to respiratory infections. Temperatures were taken and leukocyte counts made for most of them.

† None of the patients had Vincent's angina. No connection was found between the presence of spirilli and fusiform bacilli and hemolytic streptococci in cultures of the same material.

TABLE 3—*Analysis of Findings in Cultures Made from Material Taken from Throats of Young Adults Who Were Supposedly Not Ill (Chiefly Medical Students, Nurses and Hospital Technicians)*\*

Organisms Noted in 85 Cultures Made on Blood Agar	Times Found	Percentage
Cocci causing greening on blood agar (no further differentiation)	85	100
Staphylococci	39	70
Albus	40 times	
Albus haemolyticus	8 times	
Aureus	6 times	
Aureus haemolyticus	5 times	
Gram negative micrococci chiefly <i>Micrococcus catarrhalis</i> and <i>Micrococcus pharyngis sicus</i>	54	64
Hemolytic streptococci	17	20
Sarcinae	22	26
Anhemolytic streptococci	9	11
Diphtheroids	6	7
Large gram positive bacilli	6	7

\* All were questioned regarding recent respiratory infections and recent exposures to respiratory infections. Temperatures were taken and leukocyte counts made for most of them.

be appreciated by all physicians that colonies of *St. viridans* are almost invariably present in material properly taken from throats in this geographic area.

Staphylococci and gram-negative micrococci were found in the majority of cultures. Anhemolytic streptococci, while found infrequently, were thought to have no special pathologic significance. Since our chief interest in this study was in hemolytic streptococci, the significant associated clinical findings in those persons found to be harboring them are summarized in (table 4). Of 4 persons having large numbers of hemolytic streptococci—as indicated by a 3 plus or a 4 plus notation—3 had been quite recently exposed to scarlet fever. Two of these had definitely inflamed throats. The fourth was convalescent from scarlet fever. The majority of the hemolytic streptococcus carriers with less strongly positive cultures had inflamed throats and slightly elevated leukocyte counts and some had slight fever. The impression gained here that hemolytic streptococci rarely occur in large numbers in perfectly normal persons had support in studies to be shown later.

in all Forty-seven per cent of the nurses assigned to the Children's Hospital had cultures showing this type of streptococci when they arrived, indicating the high rate of exposure throughout the entire hospital Of those who entered free of these organisms, 72.6 per cent had acquired them, as revealed by cultures, at some time before they finished their service However, only 5.1 per cent of the total number of cultures were strongly positive for hemolytic streptococci, as indicated by a 3 or 4 plus recording, of the remaining ones, 13.7 per cent were 2 plus and 34.6 per cent 1 plus

A study of the physical condition of the nurses who harbored hemolytic streptococci (table 8) revealed that 47 of the group of 200 nurses had at some time one or more 3 plus or 4 plus cultures Thirty of this 47—almost two thirds—had an active infection of the nose or the throat at the time the culture was taken or had been off duty with acute sore throat or sinusitis within six weeks of that time, and 20 of them were sick enough that they had to go off duty

Sixty more nurses of the group of 200 had one or more 2 plus cultures but never any with heavier growths Only three of them were found to have frankly

TABLE 8—Study of Physical Condition of Nurses Whose Cultures Were Positive for Hemolytic Streptococci

	Number	Percentage
Total number of nurses studied	200	
Nurses having at some time 3+ or 4+ cultures	47	23.5
Nurses having 3+ or 4+ cultures who had pathologic findings in nose and throat	30	
All of these had an active infection at the time material was taken for culture or had been off duty within six weeks of that time with acute sore throat or sinusitis		
Nurses having 3+ or 4+ cultures who had to go off duty during their service at the Children's Hospital because of sore throat or sinusitis	20	
These twenty nurses lost 132 days off duty, an average of 6.6 days per nurse		
Nurses having 2+ but not 3+ or 4+ cultures	60	30% of plus culture
Nurses with 2+ cultures who had pathologic findings in nose and throat	3	
The time lost because of sore throat and sinusitis in this group was 16 days		

pathologic changes in the throat or the nose, and only these nurses were required to go off duty because of infection in these regions The physical status of those with 1 plus cultures only was not determined, because they were not required to report for examination Our records do not show that any were forced to go off duty because of infection of the upper respiratory passages Thus it appears that the majority of those persons who have large numbers of hemolytic streptococci in the throat or the nose have active infection in these areas or are convalescent from such infection

How much of a menace those persons constitute toward the persons with whom they are in contact cannot be determined from this study However, if an analogy may be drawn with another disease characterized by sore throat due to hemolytic streptococci, scarlet fever, it will be seen that the rate of spread to direct contacts is alarmingly high At the Cook County Contagious Hospital 21 per cent of the patients with scarlet fever studied over a thirteen month period had another member of the immediate household in the hospital with scarlet fever during their period of hospitalization or within a few days of the time they returned home<sup>2</sup>

<sup>2</sup> Rhoads, P. S., Tucker, W. H., and Rappaport, B. Management of Scarlet Fever Contacts, J. A. M. A. 117:1063 (Sept. 27) 1942



## CARRIERS OF HEMOLYTIC STREPTOCOCCI

That hemolytic streptococci are readily spread from one person to another is shown by the fact that 20 per cent of a group of normal young adults harbored hemolytic streptococci in their throats while 41 (53.4 per cent) of a group of 77 persons in our own practice who were directly exposed to scarlet fever were found to have these organisms in their throats. In this same connection a study of

TABLE 6—*Clinical Data on Supposedly Normal Young Adults Who Were Found to Harbor Streptococci in Their Noses*

Kind of Growth	Temperature F	White Blood Cell Count	Clinical Findings
Carriers of Hemolytic Streptococci			
1+	98.4	9,550	Acute pharyngitis 2 days after culture was taken
1+	98.6	7,650	No pathologic condition
2+	99.4	6,900	Scarlet fever 1 month previous nasal mucosa still inflamed
1 Col	98.2	6,300	Exposed to scarlet fever 2 days before no pathologic condition
Carriers of Anhemolytic Streptococci			
3+	98.6	7,800	No pathologic condition
2+	98.4	7,250	Just over a cold, mucous membranes red
4+	98.6	8,600	Chronic paranasal sinusitis
1+	99.2	No count	No pathologic condition
Carriers of Green Forming Cocci			
1+	98.4	8,200	No pathologic condition
3+	99.4	10,800	Chronic sinusitis
4+	98.9	10,000	Chronic sinusitis
1+	99	8,900	Chronic sinusitis, acute cold 1 week ago
1+	98.6	9,000	Chronic sinusitis, last acute flareup 6 weeks ago

TABLE 7—*Study of Two Hundred Nurses at Cook County Children's Hospital Who Had Cultures Made of Material from Nose and Throat When They Began Duty and at Weekly Intervals Thereafter*

	Number	Percentage
Total number of cultures	1,600	
Cultures positive for hemolytic streptococci	855	53.4
Cultures negative for hemolytic streptococci	745	46.6
Cultures 3+ or 4+ for hemolytic streptococci	82	5.1
Cultures 2+ for hemolytic streptococci	220	13.7
Cultures 1+ for hemolytic streptococci	553	34.6
Total number of nurses for whom cultures were made	200	
Nurses whose initial culture showed hemolytic streptococci	91	47
Nurses whose initial culture showed no hemolytic streptococci	109	53

Of the 109 nurses who entered with a negative culture, 77 (72.6 per cent) had hemolytic streptococci in their throats or noses before they left the Children's Hospital. (An average of eight cultures were taken per nurse.) Twenty-nine continued to have negative cultures throughout their stay.

200 nurses chosen alphabetically from the Cook County Children's Hospital is of interest (table 7).

In a previous study<sup>1</sup> we had found that sore throat due to hemolytic streptococci occurred more frequently in nurses on duty in the Children's Hospital than in any other division of Cook County Hospital save the Contagious Hospital. Dr. M. L. Blatt and his associates there wished to learn whether nurses were spreading hemolytic streptococci among the patients. As a part of this study, all nurses had cultures made of material from the nose and throat, on blood agar, when they began service and at weekly intervals thereafter. An average of eight cultures were made per nurse on the group selected for study, making 1,600 cultures.

INCIDENCE AND CLINICAL SIGNIFICANCE OF STREPTOCOCCUS VIRIDANS  
AND PNEUMOCOCCI IN CULTURES OF MATERIAL  
FROM THE NOSE

In a series of 591 cultures (table 10) of material taken from the noses of persons suffering from infections of the upper respiratory tract at all seasons of the year, only 73 (12.3 per cent) were found to contain green-forming cocci. An estimation

TABLE 10—*Analysis of Data on Nasal Cultures in Which Green-Forming Cocci Were Found*

	Number	Percentage
Total number of cultures	591	
Number in which green forming cocci were found	73	12.3
Green colonies unidentified further	18 times	
Streptococcus viridans	37 times	
Pneumococcus	21 times	
Type III	6 times	
Undetermined	5 times	
Type XXIII	3 times	
Type XXII	2 times	
Type VI	1 time	
Type XXV	1 time	
Type XIX	1 time	
Type XI	1 time	
Type VII	1 time	
Number of cultures containing green forming cocci associated with clinical findings that indicated active disease	72	93.6
Number of cultures containing green forming cocci from frankly allergic persons with exacerbation of chronic rhinitis or sinusitis	46	63
Number of cultures from children 12 years or under	115	
Number of cultures positive for green forming cocci	21	18.3
Number of cultures from adults	476	
Number positive for green forming cocci	52	10.9

TABLE 11—*Portion of Summarized Clinical Findings in Persons with Streptococcus Viridans or Pneumococci in Nasal Cultures*

Date	Initials	Age	Green Colonies Unidentified	Str Viridans	Pneumo coccus	Clinical Findings	Temperature, F
3/20/39	M A	8		++++		Acute pharyngitis and rhinitis in allergic child, white blood cell count 15,650	102
4/11/39	J B	A		+		Acute sinusitis (chronic allergic rhinitis)	98.6
4/10/39	M A	A	+-			Acute flareup of chronic allergic sinusitis	99.2
4/29/39	T T	11			Type 19	Acute exacerbation of chronic rhinitis	
5/4/39	M N	A		++	+-+	albuminuria	99.4
5/15/39	M S	A	++			Acute rhinitis with prostration	99.2
5/19/39	B C	4	+++			Chronic allergic rhinitis and iritis	99.0
5/25/39	M S	A	+++-			Acute rhinitis and tonsillitis	102.4
6/29/39	J W	8	+			Acute flareup of chronic allergic rhinitis, no fever	
10/8/39	K W	A			Type 3	Acute flareup of chronic allergic rhinitis	101.2
10/14/39	M L	A			+++	Acute sinusitis	101.0
					Type 1		
					+++	Chronic allergic state with acute sinusitis and asthma	
11/20/39	A V	6			Type 11	Acute pharyngitis and rhinitis	103.0
					++		

of the clinical significance of these organisms in this series was attempted. From 58 of the 73 cultures in which the green-forming cocci were found, four to six colonies were transferred to tubes of broth in which pneumococci were proved to grow well and the cultures were examined microscopically and for solubility in bile. In this way 21 (36.2 per cent) of the 58 cultures were identified as pneumococci and the remainder as Str. viridans. The two organisms were seldom found together in the nose.

It is seen in table 9 that often secondary cases occur after a patient has been discharged from the Contagious Hospital and returns home, at the end of twenty-eight days, as a so-called healthy carrier. How long such persons may remain carriers has not been determined in our studies, but we found by examining the records of the past five years at the Evanston Hospital that 63 per cent of the patients with scarlet fever had positive cultures at the end of their twenty-eight day quarantine. One of our private patients had strongly positive cultures for four months.

While the great practical difficulty of quarantining all persons who harbor large numbers of hemolytic streptococci in the nose and throat is thoroughly appreciated by those who have tried to quarantine even an occasional one, the necessity of dealing more adequately with the carrier problem is easily apparent. In cooperation with Dr. John Coulter, Dr. Alfred Lewy, of the staff of the Cook County Nurses' Infirmary, tried treating the nasopharynx and pharynx daily with ultraviolet rays, without ridding the throats of hemolytic streptococci. Giving sulfanilamide over as long periods as the nurses would take the drug was equally unsuccessful.

TABLE 9—Typical Sequence of Cases of Scarlet Fever in Two Families of the Cook County Hospital Series (From Rhoads, P. S., Tucker, W. H., and Rappaport, Benjamin: Management of Scarlet Fever Contacts, J. A. M. A. 117:1063-1065 [Sept. 27] 1941)

	Name	Age	Onset	Admission	Discharge
First family	Frank	6	9/14/39	9/18/39	10/13/39
	George	10	10/17/39	10/19/39	11/14/39
	Geraldine	8	10/18/39	10/19/39	11/18/39
	Lee	4	11/1/39	11/2/39	11/29/39
	Paul	8 mo	11/9/39	Cared for at home	
Second family	Lillian	9	12/9/39	12/11/39	1/6/40
	Clifton	10	1/9/40	1/13/40	2/6/40
	Mildred	13	1/14/40	1/15/40	2/11/40

In 1941 Schoenbach, Enders and Mueller<sup>3</sup> reported that tyrothricin (an extract from *Bacillus brevis* of Dubos) in a dilution of 1:100 in physiologic solution of sodium chloride with 2.5 per cent glycerin, when sprayed onto the rhinopharynx, was effective in terminating the carrier state in 5 persons convalescent from scarlet fever. This method was tried by us in the treatment of 2 nurses, but cultures of material from their throats showed no change in the numbers of hemolytic streptococci.

Placing carriers of hemolytic streptococci in environments in which they do not encounter more streptococci is an important part of the regimen to rid them of the carrier state.

Daily spraying of the throat and the nose with a 2.5 per cent solution of sodium sulfathiazole (2-[paraaminobenzenesulfonamido]-thiazole) or of sodium sulfadiazine (2-[paraaminobenzenesulfonamido]-pyridine) has appeared to terminate the carrier state in 9 persons.<sup>4</sup> In others a combination of spraying of the nose and throat with a solution of a sulfonamide compound and administering of sulfadiazine by mouth has appeared to help. But none of these methods is uniformly effective.

3 Schoenbach, E. B., Enders, J. F., and Mueller, J. H.: The Apparent Effect of Tyrothricin on *Streptococcus Hemolyticus* in the Rhinopharynx of Carriers, *Science* 94:217 (Aug. 29) 1941.

4 This statement is based on work to be reported in another article.

However, green-forming cocci, as well as hemolytic streptococci, when found in cultures of material from the nose were nearly always associated with frank infection of the nasal mucosa, the sinuses or the nasopharynx

Among persons directly exposed to hemolytic streptococcus infections (such as those coming in contact with patients suffering from scarlet fever or nurses on duty in children's hospitals) the incidence of hemolytic streptococci in cultures of material from the throat and the nose was more than 50 per cent, while in an average group of young adults it was 20 per cent

There is abundant evidence that so-called healthy carriers spread scarlet fever. The assumption is reasonable that carriers of nonspecific hemolytic streptococci also spread infection to those with whom they come in contact

No uniformly successful method of ridding carriers of hemolytic streptococci has been found by us

While green-forming cocci are regarded as normal inhabitants of the throat, they were rarely found in the nose except in association with definite infection of the nasal mucosa or sinuses. They were found more frequently in children's colds than in those of adults

#### CONCLUSIONS

Hemolytic streptococci are responsible for about two thirds of the attacks of tonsillitis, pharyngitis, laryngitis and sinusitis in young adults. These diseases are probably more frequent and cause more disability than any other diseases affecting this age group

Persons who harbor large numbers of hemolytic streptococci in their throats and those who harbor these organisms or green-forming cocci in their noses usually have an active infection or are convalescent from an active infection

The serious results of allowing carriers of hemolytic streptococci to circulate in groups of young adults, such as soldiers in barracks, is apparent

Cultures of material from the throat and the nose on blood agar are inexpensive and easy to make, and not difficult to interpret. They should be made in all instances of infection of the throat or the nose

Serious consideration should be given to quarantining of persons harboring hemolytic streptococci in the throat or the nose or green-forming cocci in the nose. More effective methods of ridding carriers of these organisms urgently need to be devised

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Type III was the most frequent type of *Pneumococcus* found—the rest of the 21 cultures being widely scattered among the other types. None of the patients had pneumonia at the time the cultures were taken—which probably accounts for the fact that types I and II were not encountered.

The striking facts brought out by the clinical findings in these persons (table 11) are that nearly all persons harboring green-forming cocci in the nose are ill or recovering from acute infection of the nose and the throat and that a high percentage are frankly allergic. Whether the infection with these organisms is the result of the allergic state or the cause of it was not determined in our studies. Another interesting finding was the much greater frequency of green-forming cocci in children's noses than in those of adults. We had the impression that this was true but had no confirmation of the fact until this study was made. A possible explanation may lie in the shorter distance in children from the nasopharynx to the nares. Possibly the swab more often reaches the natural habitat of these organisms in young persons. Our results are in agreement with those of Jacobson and Dick,<sup>5</sup> who found that green-forming cocci were rarely present in nasal cultures in the absence of acute rhinitis and/or paranasal sinusitis. They also noted that children harbored these organisms in the nose more frequently than adults.

#### SUMMARY

In a nursing group averaging 1,054, over a five year period the average number off duty at all times because of infection of the upper respiratory tract was 4 per cent of the entire number. Of the ones so disabled, 65 per cent were thought to have bacterial infections, including acute tonsillitis, pharyngitis, laryngitis, purulent rhinitis and paranasal sinusitis. The other 35 per cent had simple rhinitis, influenza or grip—all thought to be virus infections. The peak of the bacterial infections of the nose and throat was in January, February, March and April, while the peak of the virus infections was in December—at which time the incidence always rose sharply.

Among a group of nursing students studied through their three years of training, the average time lost because of bacterial infections of the nose and throat was 20.46 days—27 per cent of the total time lost by them because of illnesses of various types.

Sixty-six per cent of these infections appeared to be caused by hemolytic streptococci. The average time off duty caused by each attack of sore throat or sinusitis due to hemolytic streptococci was 16.85 days.

The complications resulting from these infections caused by hemolytic streptococci were almost as numerous as those in a series of patients with scarlet fever of the same age, studied over the same period, though not as serious.

Among normal young adults (chiefly medical students) 20 per cent were found to harbor hemolytic streptococci. Those whose cultures contained large numbers of hemolytic streptococci were found often to have inflammation of the throat or the nose, slight fever and leukocytosis. Others were convalescent from recent infections. In no instances were normal-appearing mucous membranes found to contain hemolytic streptococci in large numbers.

Green-forming cocci (*Str. viridans* and/or pneumococci) were found in every culture made of material swabbed from the throat. They were therefore regarded as normal inhabitants of the pharynx.

5 Jacobson, L. O., and Dick, G. F. Normal and Abnormal Bacterial Flora of the Nose. *J. A. M. A.* 117:2222 (Dec. 27) 1941.

of the test. The bladder was emptied. A 0.5 cc dose of solution of posterior pituitary of twice U. S. P. strength (10 U. S. P. posterior pituitary units) or occasionally a similar amount of pitressin was injected subcutaneously. The urine was collected in one and two hours. The higher specific gravity was recorded.

In both tests the specific gravity was measured in a calibrated urinometer and corrections made for albuminuria and temperature. None of the specimens exhibited sugar.

In 11 cases the test with solution of posterior pituitary was compared with a phenol-sulfonphthalein test. For the latter the method of Chapman and Halsted<sup>3</sup> was used. The bladder was emptied, 600 cc of water was ingested and thirty minutes later 1 cc of phenol-sulfonphthalein solution (6 mg) was injected intravenously. Urine was collected in fifteen minutes and one hour. However, only the result for the fifteen minute sample was recorded as it was the more significant one.

This comparison with this phenolsulfonphthalein test was included because Goldring, Clarke and Smith<sup>4</sup> showed that at the low concentration in the plasma occurring in the test about 94 per cent of the phenolsulfonphthalein is excreted by tubular secretion and only 6 per cent by glomerular filtration.

### RESULTS

A comparison of the maximum values obtained in the test with solution of posterior pituitary and the Fishberg test for 67 subjects is recorded in the tables. The two concentration tests gave similar results. The first test gave slightly higher values in the majority of cases. For the 6 subjects without renal or vascular

TABLE 1—*Normal Subjects (Persons Without Vascular or Renal Disease)*

Subject	Age	Blood Pressure	Fishberg Test	Test with Solution of Posterior Pituitary	Mosenthal Test	Comment
1	18	110/70	1.027	1.026		
2	43	120/80	1.023	1.025		
3	18	122/80	1.026	1.026		
4	25	128/88	1.019	1.027		
5	30	120/90	1.027	1.031		
6	55	100/80	1.020	1.022		

disease (table 1) the values were above 1.022, in keeping with the normal figures published by Sodeman and Engelhardt<sup>2</sup> and Fishberg.<sup>1</sup>

The 43 patients with hypertension or hypertensive heart disease but without renal impairment (table 2) had values above 1.020. Here again there was fairly close similarity with the Fishberg test. The greatest variation was 0.013. In most cases of variation the Fishberg test gave a lower value than the test with solution of posterior pituitary. In 5 cases the Fishberg test gave a result below 1.020 whereas the test with posterior pituitary solution gave a normal result and no other evidence of renal impairment existed.

The 15 patients with definite impairment of renal function (table 4), consisting of 9 with malignant hypertension and 2 with chronic glomerulonephritis, had maximum values for specific gravity below 1.020 in both the Fishberg test and the test with posterior pituitary solution. The comparative results were extremely close, the greatest variation being 0.004.

Only 4 subjects with congestive heart failure were available (table 3). In all 4 the solution of posterior pituitary seemed to give a maximum concentration even in the presence of edema. Although an exact comparison was not available, usually because the edema disappeared too rapidly, my previous experience with the Fish-

3 Chapman, E. M., and Halsted, J. A. Fractional Phenolsulphonephthalein Test in Bright's Disease, *Am J M Sc* **186** 223-232 (Aug.) 1933.

4 Goldring, W., Clarke, R. W., and Smith, H. W. Phenol Red Clearance in Normal Man, *J Clin Investigation* **15** 221-228 (March) 1936.

# A RENAL CONCENTRATION TEST USING SOLUTION OF POSTERIOR PITUITARY

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The ability of the renal tubules to concentrate urine is the basis of several clinical tests of renal function in use today. Fishberg<sup>1</sup> expressed the belief that the specific gravity tests are the most useful tests of renal function available for the general practitioner and general hospital use. Sodeman and Engelhardt<sup>2</sup> recently advocated use of solution of posterior pituitary for a renal function test. This test utilizes the antidiuretic principle of the posterior lobe of the pituitary gland and enables one to perform a renal concentration test without prolonged restriction of the intake of fluids. It has the further advantage of giving reliable results in the presence of ascites or cardiac edema, where other concentration tests cannot be used because of the impossibility of depriving the kidneys of the excess fluid already available in the body. The latter point is important in deciding whether the function of the kidneys is good enough to permit the use of a mercurial diuretic in a patient with congestive heart failure that has not responded to the usual methods of treatment.

Sodeman and Engelhardt<sup>2</sup> have shown that in normal persons 0.5 cc of solution of posterior pituitary of twice U. S. P. concentration (10 U. S. P. posterior pituitary units) injected subcutaneously will inhibit the diuresis normally produced by the ingestion of 1,600 cc of water in fifteen minutes. They have further reported that maximum concentration occurs within the first two hours after the injection of the solution and that 1 cc of the solution (20 posterior pituitary units) or a previous period of restriction of the intake of fluids or of deprivation of fluids does not further elevate the specific gravity of the urine passed. There is a similar antidiuretic effect in patients with cardiac edema. In normal persons they found that the specific gravity varies from 1.023 to 1.040, whereas in patients with impaired renal function the maximum specific gravity is considerably reduced. In their papers they were more interested in the increase in the specific gravity of the urine passed before and after the injection of the solution of posterior pituitary than in a comparison of their test with a standard concentration test.

It seemed desirable to repeat this work and to compare their test with a standard renal concentration test in a study of a large number of persons with and without impaired renal function.

## TECHNIC

The Fishberg<sup>1</sup> renal concentration test was used, in which no fluids are allowed from 5 p. m. of the previous evening until 9 a. m. of the morning of the test. Less than 200 cc of fluid was allowed with the evening meal, which was high in protein content. The evening meal was eaten about 4:30 p. m. All overnight urine was discarded. Urine specimens were collected at 7, 8, and 9 a. m. and the highest specific gravity recorded.

The test with solution of posterior pituitary was done without special preparation either in the morning or the afternoon. No food or fluid was allowed during the two hour period

1 Fishberg, A. M. Hypertension and Nephritis, ed. 4, Philadelphia, Lea & Febiger, 1939, p. 74.

2 Sodeman, W. A., and Engelhardt, H. T. (a) A Renal Concentration Test Employing Post Pituitary Extracts. Response of Normal Subjects, *Proc Soc Exper Biol & Med* **46** 688-691 (April) 1941, (b) A Renal Concentration Test Employing Posterior Pituitary Extract, *Am J M Sc* **203** 812-818 (June) 1942.

almost a year and had been treated by administration of digitalis and restriction of fluids. His edema and symptoms were markedly improved by the use of mercurial diuretics. Hence cardiac failure was a prominent factor in the impairment of his renal function.

In the 11 cases in which the test with solution of posterior pituitary was compared with the intravenous phenolsulfonphthalein test (table 5), the results were similar. By the technic used, the normal person excretes an average of 35 per cent

TABLE 4—*Subjects with Definitely Impaired Renal Function*

Subject	Age	Blood Pressure	Fishberg Test	Test with Solution of Posterior Pituitary	Mosenthal Test	Comment
53	47	200/120	1 011	1 011		
54	45	170/110	1 015	1 015		
55	53	240/160	1 015	1 015		Died in uremia 4 weeks later
56	48	240/150	1 023	1 026		
		280/180	1 011	1 015		6 weeks later, died in uremia 3 months later
57	48	180/110	1 014	1 018	1 015	
58	44	260/150	1 010	1 010		
59	48	180/130	1 018	1 017		
60	48	224/170	1 010	1 009		Died in uremia
61	44	200/150	1 015	1 017		
		244/180		1 012		4 weeks later died in uremia 1 month later
62	50	180/110	1 019	1 016		
63	48	158/110	1 016	1 016		
64	46	140/80	1 013	1 014		
65	66	240/150	1 014	1 012		
66	55	166/88	1 014	1 012		
67	29	230/165	1 013	1 013		

TABLE 5—*Comparison of Result of Test with Solution of Pituitary and Intravenous Phenolsulfonphthalein Test*

Subject	Diagnosis	Test with Solution of Posterior Pituitary	Intravenous Injection of Phenolsulfonphthalein (Percentage Excreted After 15 Min.)	Comment
3	Normal	1 026	40	
43	Hypertension	1 025	30	
44	Hypertension	1 023	30	
45	Hypertension	1 027	30	
46	Hypertension	1 024	35	
47	Hypertension	1 025	50	
48	Hypertensive heart disease	1 027	37	
49	Hypertensive heart disease	1 028	40	
50	Hypertensive-arteriosclerotic heart disease	1 022	15	Chronic congestive heart failure
53	Chronic glomerulonephritis with congestive heart failure	1 011	25	
66	Hypertension and chronic pyelonephritis	1 012	10	

of the dye in the first fifteen minutes, any amount less than 25 per cent is considered abnormal.

#### EFFECT OF SOLUTION OF POSTERIOR PITUITARY ON HYPERTENSION AND THE CORONARY ARTERIES

Sodeman and Engelhardt<sup>2b</sup> observed no significant rise in blood pressure with 0.5 cc. of solution of posterior pituitary of twice U. S. P. strength (10 U. S. P. posterior pituitary units). Goodman and Gilman<sup>5</sup> stated that in the normal subject

<sup>5</sup> Goodman, L., and Gilman, A. The Pharmacological Basis of Therapeutics, New York, The Macmillan Company, 1941, pp. 647 and 664.



berg test indicates that that test is not reliable in the presence of a reservoir of excess fluid in the body. In the case of subject 50, the specific gravity with the test with posterior pituitary solution was 1.022 and that with Fishberg test 1.023,

TABLE 2—*Subjects with Hypertension Without Renal Impairment*

Subject	Age	Blood Pressure	Fishberg Test	Test with Solution of Posterior Pituitary	Mosenthal Test	Comment
7	44	150/110	1.021	1.020		
8	45	160/110	1.025	1.024		
9	52	200/110	1.020	1.023		
10	51	210/110	1.021	1.025		
11	51	220/120	1.018	1.023	1.024	
12	43	206/136	1.021	1.024		
13	46	170/110	1.018	1.023		
14	50	204/122	1.021	1.023		
15	45	200/130	1.016	1.022		
		150/110	1.024	1.023		5 months later
16	46	190/130	1.024	1.027	1.027	
17	48	178/120	1.020	1.027		
18	51	170/120	1.027	1.022		
				1.025		2 weeks later
19	48	210/250				
		110-160	1.020	1.026	1.024	
20	44	234/160		1.019		
		220/130	1.023	1.021		1 month later
21	48	190/110	1.032	1.030		
22	17	150/95	1.029	1.026		
23	44	180/145	1.020	1.022		
24	49	190/130	1.025	1.026		
25	45	190/130	1.022	1.022		
26	46	210/120	1.023	1.023		
27	45	190/100	1.023	1.022		
28	41	190/120	1.026	1.025		
29	49	175/105	1.020	1.020		
30	46	178/110	1.024	1.027		
31	48	140/100	1.023	1.022		
32	48	170/120	1.029	1.024		
33	53	200/110	1.030	1.030		
34	54	155/110	1.024	1.022		
35	55	150/100		1.017		Drank 1 glass of water during test
	55	150/100	1.022	1.028		
36	42	180/120	1.031	1.030		
37	56	180/110	1.022	1.021		
38	47	200/100	1.026	1.028		
39	45	220/140	1.030	1.022		
				1.023		Next day
40	49	155/105	1.017	1.030		
41	53	190/220	1.019	1.023		
		120/150				
42	62	214/124	1.022	1.028		
43	45	160/110	1.026	1.025		
44	48	185/100	1.023	1.023		
45	53	170/110	1.022	1.027		
46	46	150/100	1.023	1.024		
47	50	170/90	1.026	1.025		
48	49	205/120	1.021	1.027		
49	51	174/110	1.023	1.028		

TABLE 3—*Subjects with Congestive Heart Failure*

Subject	Age	Blood Pressure	Fishberg Test	Test with Solution of Posterior Pituitary	Mosenthal Test	Comment
50	53	155/105	1.023	1.022		Slight edema
51	51	200/30		1.017		Marked edema
			1.015			No edema
52	55	210/85		1.019		Marked edema
			1.017	1.019		No edema
53	47	220/120	1.004	1.011		Congestive heart failure with edema during diuresis
			1.011	1.011		No edema

whereas the phenolsulfonphthalein excreted in fifteen minutes was only 15 per cent and the nonprotein nitrogen content of the blood was 50 mg per hundred cubic centimeters. This patient had been in a state of chronic congestive heart failure for

Contraindications for this test are pregnancy and coronary heart disease, especially acute myocardial infarction. In the presence of angina pectoris without recent infarction the test should be used with extreme caution.

#### SUMMARY AND CONCLUSIONS

A renal concentration test using solution of posterior pituitary is described. This test is applicable without the necessity of previously depriving the patient of water and in the presence of edema or ascites. The results obtained for normal subjects, for patients suffering from hypertension without impairment of renal function, and for patients who had impaired renal function compare favorably with the results obtained with the Fishberg and phenolsulfonphthalein tests. The advantages and contraindications are described.

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no rise in blood pressure occurs from the injection of solution of posterior pituitary. I checked the blood pressure in 6 patients with hypertension in whom the readings had ranged from 170 systolic and 120 diastolic to 260 systolic and 170 diastolic, with the patients resting quietly in bed during the procedure. In most of these subjects there was a slight rise in the blood pressure in the first fifteen minutes over the initial resting pressure, but in no case did it go above the usual pressure the patient maintained when he was up and about. None of the patients on whom the test with solution of posterior pituitary was done complained of distressing symptoms. Graybiel and Glendy<sup>6</sup> who injected a dilute solution of pitressin intravenously until distressing abdominal cramps were produced, found only slight changes in pulse rate, blood pressure, cardiac output and metabolic rate in normal persons, in patients with hypertension and in patients with angina pectoris.

Solution of posterior pituitary and pitressin are known to constrict the coronary arteries and this should contraindicate their use in patients with disease of those arteries. My subject 37 had hypertensive arteriosclerotic heart disease with angina class III. Anginal symptoms were produced by slight effort, such as walking up a short flight of stairs. For this patient I used the test with solution of posterior pituitary with extreme caution. He remained in bed for thirty minutes after the injection of 0.5 cc of the solution. He had no discomfort. After he was up and about for fifteen minutes, he felt slight substernal distress and tingling down the left arm. These symptoms promptly disappeared after he used glyceryl trinitrate. Graybiel and Glendy<sup>6</sup> in the aforementioned studies, using an intravenous injection of pitressin, found that anginal pain was not reproduced in 2 patients with severe angina pectoris. They concluded "that pitressin in amounts sufficient to provoke distressing abdominal cramps does not significantly decrease the blood supply to the myocardium in relation to the work of the heart, and that it is safe and practical to give pitressin to patients with coronary heart disease."

#### COMMENT

This test of renal function promises to be an excellent addition to the standard concentration tests. It seems to be as reliable as the Fishberg test. Its advantages are several. It eliminates the necessity of the patient's cooperating in a prolonged deprivation of fluids. This is important in dealing with an unintelligent or an uncooperative patient such as is often seen in clinic or general hospital practice. It is useful in office practice, saving the patient an extra trip and the necessity of carrying several bottles of urine. Another important advantage is its usefulness in the presence of a reservoir of fluid in the form of ascites or edema, making restriction of fluids impossible. In such a case a prompt estimation of renal function can be obtained. It has been my practice to withhold mercurial diuretics from patients in whom there is an inability to concentrate urine to 1:016. If a patient with congestive heart failure has a test showing good concentration of urine (subject 50), even though he has retention of nitrogen, it is safe to use mercurial diuretics.

The mechanism of the antidiuretic action of solution of posterior pituitary is discussed by Goodman and Gilman<sup>5</sup>. The site of action is thought to be the loop of Henle of the renal tubule. This antidiuretic effect is essential for physiologic reabsorption of water by these cells. Solution of posterior pituitary will inhibit water diuresis, but xanthines and mercurial diuretics counteract this antidiuretic action, and one should be careful to omit these drugs before using the posterior pituitary test for renal function.

<sup>6</sup> Graybiel, A., and Glendy, R. E. Circulatory Effects Following the Intravenous Administration of Pitressin in Normal Persons and in Patients with Hypertension and Angina Pectoris, *Am Heart J* 21: 481-489 (April) 1941.

oral administration, while four to seven hours later the drug can no longer be found.<sup>3</sup> In the urine the alkaloid appears within two to three hours after oral administration and traces can be detected up to twelve to twenty-four hours.<sup>4</sup> If a cinchona derivative is administered in divided doses, the maximum concentration is found in the blood<sup>1a</sup> or myocardium<sup>3</sup> about one to two hours after the last dose. Under these conditions a larger total amount is excreted in the urine<sup>5</sup> and a smaller amount is found in the myocardium<sup>3</sup> than when the same total amount is given as one single dose.

*Clinical Studies*—When a cinchona derivative is given to a patient with auricular fibrillation or flutter,<sup>6</sup> a slowing of the auricular rate and an increase in the ventricular rate have been observed. These effects become evident about one-half hour after administration of a single dose by mouth, reach a maximum in two to three hours and begin to decrease about one hour later. They are still present eight hours after administration of the drug but are not apparent in twenty-four to thirty hours. When quinidine is given intravenously, the maximum slowing of the auricles occurs within ten minutes and persists for ten to fifteen minutes, after which the auricular rate increases slowly, returning to the original level after five hours in most cases.<sup>7</sup>

Similar information is obtained by observation of the ventricular rate during quinidine therapy of ventricular tachycardia. Scott<sup>8</sup> reported on 1 patient in whom such paroxysms could be terminated invariably one-half to one hour after the oral administration of 0.4 Gm of quinidine sulfate. Riseman and Linenthal,<sup>9</sup> in treating a patient with ventricular tachycardia of eight and one-half days' duration, observed that the effect of each dose (quinidine sulfate by mouth or quinine dihydrochloride intramuscularly) became evident in one-half to one hour and reached its maximum within two hours, following which the effect decreased so that after approximately ten hours it was negligible.

Wilson and Wishart<sup>7</sup> found that when quinidine was given intravenously to patients with auricular fibrillation the response occurred within ten minutes and the magnitude of effect was about twice as great as when given orally. Because the toxic effects were so great, these investigators concluded that intravenous administration "promises comparatively little from the standpoint of practical therapeutics." Hepburn and Rykert<sup>10</sup> treated 9 patients with ventricular tachycardia

3 Weisman, S. A. Studies on the Time Required for the Elimination of Quinidine from the Heart and Other Organs, *Am Heart J* **20** 21, 1940.

4 (a) Lewis, T., Drury, A. N., Wedd, A. M., and Iliescu, C. C. Observation upon the Action of Certain Drugs upon Fibrillation of the Auricles, *Heart* **9** 207, 1922. (b) Lewis, T. The Value of Quinidine in Cases of Auricular Fibrillation and Methods of Studying the Clinical Reaction, *Am J M Sc* **163** 781, 1922. (c) Wedd, A. M., and Hubbard, R. S. Notes on Dosage and Excretion of Quinidine Sulfate, *Clifton M Bull* **15** 69, 1929.

5 Wiechmann, E. Ueber die Ausscheidung des Chinidins im Harn, *Ztschr f d ges exper Med* **7** 155, 1919.

6 (a) Wedd, A. M. Notes on the Action of Certain Drugs in Clinical Flutter, *Heart* **11** 87, 1924. (b) Scott, R. W. Clinical Observations on Quinidine, *J Pharmacol & Exper Therap* **19** 264, 1922. (c) Lewis, Drury, Wedd and Iliescu.<sup>4a</sup> Lewis<sup>4b</sup>.

7 Wilson, F. N., and Wishart, S. W. The Effects Produced by the Intravenous Injection of Quinidin and Other Drugs upon the Mechanism of the Heart Beat, *Tr A Am Physicians* **41** 55, 1926.

8 Scott, R. W. Observations of a Case of Ventricular Tachycardia with Retrograde Conduction, *Heart* **9** 297, 1922.

9 Riseman, J. E. F., and Linenthal, H. Paroxysmal Ventricular Tachycardia, *Am Heart J* **22** 219, 1941.

10 Hepburn, J., and Rykert, H. E. The Use of Quinidine Sulfate Intravenously in Ventricular Tachycardia, *Am Heart J* **14** 620, 1937.

# STUDIES ON THE ACTION OF QUINIDINE IN MAN

## I MEASUREMENT OF THE SPEED AND DURATION OF THE EFFECT FOLLOWING ORAL AND INTRAMUSCULAR ADMINISTRATION

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The value of quinidine in the treatment of certain acute cardiac arrhythmias is well recognized. There are numerous references in the literature about the use of quinidine in treating chronic auricular fibrillation. In this condition, however, conversion to normal sinus rhythm is not urgent, and the dose of quinidine may be gradually increased over a period of days, if necessary, until the desired effect is obtained. In the acute or paroxysmal arrhythmias (auricular tachycardia, auricular fibrillation, ventricular tachycardia, etc.) the abnormal rate and rhythm may cause cardiac pain, intense palpitation, dyspnea, faintness, vomiting, pulmonary edema, collapse and even death. Prompt treatment may be essential. Proper management of such conditions requires accurate knowledge of the speed and duration of action of the therapeutic agents employed. Little exact information is available, however, concerning the factors which determine the optimum methods for employing quinidine under such conditions.

The purpose of this communication is to present measurements of the speed and duration of action of cinchona derivatives in subjects with normal cardiac rhythm. Different preparations of quinidine and quinine have been used, the dose was varied, and the drugs were administered by mouth and also by intramuscular injection. The effects of quinidine and quinine on the heart were studied by means of changes in the electrocardiogram induced by these drugs.

### REVIEW OF THE LITERATURE

The speed of onset and the duration of action of quinidine have been studied by determining the concentration in the blood stream, the concentration in the cardiac musculature, the rate of excretion in the urine, the changes in the heart rate observed in patients with various arrhythmias and the changes produced in the electrocardiogram. The results of these studies are confusing.

*Laboratory Studies*—In the blood stream of man or laboratory animals very little of the drug can be detected five to ten minutes after the oral or intravenous administration of a single dose of quinidine<sup>1</sup> or quinine<sup>2</sup>. In the myocardial tissue of dogs the maximum concentration is reached within one-half to one hour after

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1 (a) Weisman, S. A. Further Studies in the Use of Quinidine in the Treatment of Cardiac Irregularities, *Minnesota Med* **22** 385, 1939. (b) Weiss, S., and Hatcher, R. A. Studies on Quinidin, *J. Pharmacol. & Exper. Therap* **30** 335, 1927.

2 (a) Hatcher, R. A., and Gold, H. Studies on Quinin, *J. Pharmacol. & Exper. Therap* **30** 347, 1927. (b) Hatcher, R. A., and Weiss, S. Studies on Quinin, *ibid* **29** 279, 1926.

findings after the giving of therapeutic doses to human beings have been a flattening, broadening and occasional notching of the T wave and an increase in the duration of the QT interval (the duration of electrical systole of the ventricle, measured from the beginning of the QRS complex to the end of the T wave)

Mahei, Sullivan and Scheribel<sup>16c</sup> have utilized the qualitative changes in the contour of the T wave to determine the speed and duration of action of quinidine. With intravenous administration of 3 grains (0.2 Gm) of quinidine sulfate in 20 cc of distilled water, these changes in the T wave were observed within a few minutes and persisted for at least three hours. After oral administration (quinidine sulfate, 10 grains [0.65 Gm] three times a day or 15 grains [1 Gm] four times a day, for five to nineteen days) the changes in the T wave were observed to begin in twelve to seventy-two hours and to disappear after several days.

#### METHODS AND MATERIAL

Sixteen hospitalized subjects with normal sinus rhythm were used in these studies. One had angina pectoris, 2 had had paroxysmal arrhythmias, 2 had hypertension and 11 had no evidence of cardiac disease, 1 was known to have achlorhydria. Eleven were men, and 5 were women. The ages varied from 17 to 68 years, 10 were over 45. Standard four lead electrocardiograms showed no evidence of coronary artery disease.

All studies were carried out in a uniform manner. A control four lead electrocardiogram was obtained. The medication was then administered and electrocardiograms were made every fifteen minutes for the first hour and then at less frequent intervals for a total of eight to fifteen hours. An additional tracing was taken twenty-four hours after the administration of the drug. The patients remained in bed except for lavatory privileges while the studies were carried out and were recumbent for at least five minutes before each tracing was obtained. No attempt was made to control the diet. Use of all drugs which might have some effect on the heart or electrocardiogram were omitted during the period of study except those being investigated. At least forty-eight hours was allowed to elapse before these studies were repeated on any person.

The effect of the following medication was studied: quinidine sulfate, single doses by mouth of 3, 5, 9, 10 or 15 grains, quinine sulfate, 5 grains by mouth, injectable quinidine (quinidine hydrochloride with urea and antipyrine), 5 grains intramuscularly, quinidine sulfate, repeated doses by mouth of 3 grains at intervals of one, two, four or eight hours or of 5 grains every four hours for two doses, quinidine hydrochloride with urea and antipyrine, intramuscular injections every two hours for five doses.

A total of 68 tests were performed. In 36 tests the three conventional leads and a precordial lead (IVR) were used (452 four lead tracings). In the remaining 32 tests lead II only was used (742 one lead tracings). In determining the duration of the QT interval seven to ten consecutive complexes were estimated to 0.01 second and the average was obtained. The variation in duration of consecutive QT intervals was 0.01 second. When the tests were repeated on different days the average of the duration of seven to ten consecutive complexes differed by less than 0.01 second.

#### RESULTS

In all 68 tests the effect of the cinchona derivatives was evidenced by a prolongation of the QT interval. In 61 tests the effect of medication was also evidenced by striking qualitative changes in the T wave. These did not lend themselves to a quantitative estimation of the frequency, degree, duration or time of onset of the quinidine effect, furthermore, they appeared later and disappeared earlier than the change in the duration of QT. These changes were observed in all four leads. The qualitative changes in the T waves were most striking in lead IVR (chart 1), but the termination of the T wave in this lead and also in lead III was not sufficiently

M. Sc. **187** 23, 1934. (f) Aschenbrenner, R. Ueber das Digitalis-Elektrocardiogram, *Klin. Wchnschr.* **15** 1039, 1936. (g) Landau, N. Ueber die Verlängerung der Systole bei Tetame und ihre Beeinflussung durch verschiedene Pharmaca, *ibid.* **17** 93, 1938. (h) Freedberg, A. S., Riseman, J. E. F., and Spiegel, I. Objective Evidence of the Efficacy of Medicinal Therapy in Angina Pectoris, *Am. Heart J.* **22** 494, 1941.

by administering a 10 to 12 per cent solution of quinidine sulfate in 5 per cent dextrose solution at a rate of 100 to 120 cc per hour. The average dose was slightly less than 20 grains (1.3 Gm.)

The conditions under which such clinical studies were carried out do not lend themselves to accurate or prolonged study of the speed and duration of action of the drug used. As a result there is no uniformity of opinion as to the optimum methods of their use.

*Choice of Preparation*—Frey<sup>11</sup> and later Lewis, Drury, Wedd and Ilescu<sup>4a</sup> found that quinidine was more effective than quinine in the treatment of auricular fibrillation. Grant and Ilescu<sup>12</sup> found quinidine more effective than cinchonidine, cinchonine or quinine.

Wiechmann<sup>5</sup> concluded that the sulfate was more readily absorbed than the alkaloid, for he found greater urinary excretion following administration of the salt. Lewis and his co-workers<sup>4a</sup> found no difference in the response to the sulfate, the bisulfate and the dihydrochloride of quinidine given orally and suggested that all are converted to the hydrochloride in the stomach.

The choice of preparation at present is limited. Practically all the drug is imported, the American pharmaceutical houses acting as distributing agents. The alkaloid, the sulfate and the hydrochloride are available, the relatively insoluble sulfate being most generally used. The more soluble dihydrochloride and citrate, which might be more suitable for injection, are not available. The formula for the injectable quinidine hydrochloride with urea and antipyrine<sup>13</sup> used in the present study was suggested by the Cinchona Institute. So far as is known, it has not been used previously, but it is similar to a preparation of quinine hydrochloride with urea and antipyrine which has been used in treating certain infectious diseases.<sup>14</sup>

*Electrocardiographic Studies*—Electrocardiographic changes have been observed following the administration of quinine<sup>15</sup> and quinidine<sup>16</sup>. The most consistent

11 Frey, W. Ueber Vorhofflimmern beim Menschen und seine Beseitigung durch Chinidin, Berl klin Wchnschr **55** 450, 1918.

12 Grant, R. T., and Ilescu, C. C. Comparison on the Action of Quinidine with Other Cinchona Alkaloids in Auricular Fibrillation, Heart **9** 289, 1922.

13 Quinidine hydrochloride 15 Gm, urea 20 Gm, antipyrine 15 Gm and distilled water to make 100 cc.

14 (a) Zuelzer, G. Zur Schlarlachfrage, Berl klin Wchnschr **56** 1131, 1919. (b) Cahn-Bronner, C. E. Die Behandlung der Lungentzündung mit subkutanen Chinininjektionen, Ztschr f klin Med **87** 292, 1919. (c) Schwarze. Ueber lokale Behandlung des Keuchhustens, Fortschr d Med **44** 1014, 1926.

15 (a) Hecht, A. F., and Matkow, J. Intravenöse Chinininjektionen bei Malaria-kranken, Wien klin Wchnschr **30** 169, 1917. (b) Hecht, A. F., and Rothberger, C. J. Experimentelle Beiträge zur Kenntnis der Chininwirkung bei Herzflimmern, Ztschr f d ges Med **7** 134, 1919. (c) Singer, R., and Winterberg, H. Chinin als Herz- und Gefässmittel, Wien Arch f inn Med **3** 329, 1922. (d) Miki, Y. Experimentelle und klinische Untersuchungen über die Dauer des K-Ekg (Kammer-Elektrokardiogramms), Ztschr f d ges exper Med **27** 323, 1922. (e) Hughes, T. A. Effect of Intravenous Injections of Quinine on Electrocardiogram in Man, Indian J M Research **19** 113, 1931. (f) Aschenbrenner, R. Ueber die Beeinflussung der Herzstromkurve und andere Nebenwirkungen bei der Chinin-Therapie, Klin Wchnschr **16** 1750, 1937.

16 (a) Schott, E. Zur Frage der Chinidintherapie, Deutsches Arch f klin Med **134** 208, 1920. (b) Cohn, A. E., and Levy, R. L. Experimental Studies on the Pharmacology of Quinidine, Proc Soc Exper Biol & Med **8** 283, 1920-1921. (c) Korns, H. M. An Experimental and Clinical Study of Quinidine Sulfate. I. Experimental, Arch Int Med **31** 15 (Jan) 1923. (d) Pardee, H. E. B. Clinical Aspects of the Electrocardiogram, New York, Paul B. Hoeber, Inc., 1933. (e) Maher, C. C., Sullivan, C. P., and Scheribel, C. P. Effect upon Electrocardiogram of Patients with Regular Rhythm of Quinidine Sulfate, Am J

In general, as the dose was increased the degree and duration of the effect were also increased and the effect became evident more rapidly. The variation of response to single doses in the subjects studied is shown in table 1. After the administration of 10 or 15 grains, 4 of the 6 patients showed slight but definite prolongation of the QT interval within fifteen minutes, only 1 patient showed a similar response to

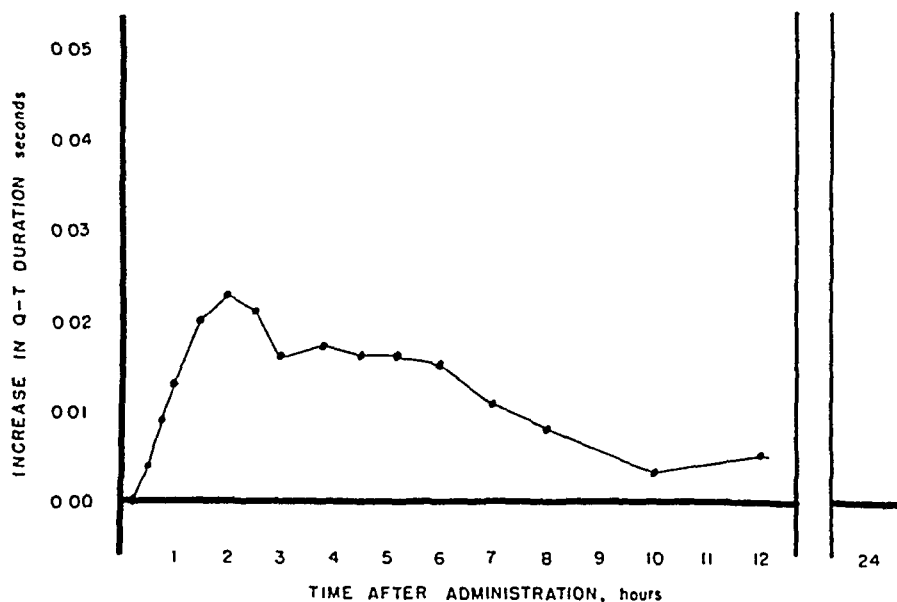


Fig 2—Electrocardiographic response to a single 3 grain dose of quinidine sulfate given by mouth (average of results obtained in 11 patients)

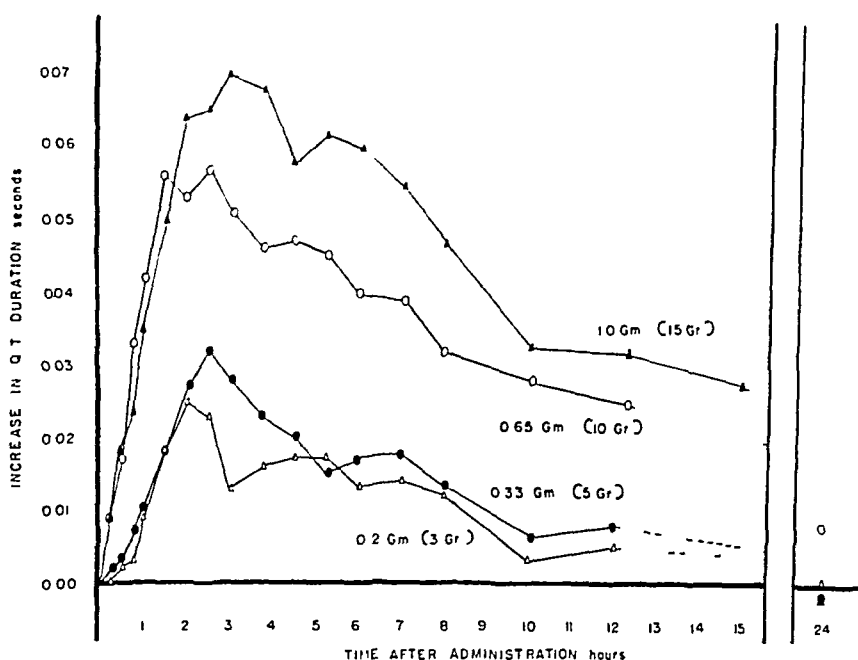


Fig 3—The comparative effects of single doses of 3, 5, 10 and 15 grains of quinidine sulfate given by mouth (average of results obtained in 6 patients)

5 grains, while no patient showed so rapid a response to 3 grains. The maximum effect was reached in one and one-half to three and three-fourths hours, irrespective of the amount of drug administered.

One of the 10 patients who received a single 5 grain dose of quinidine sulfate had pernicious anemia and complete achlorhydria. The effect in this patient was similar to that observed in the remaining 9 patients.



definite to make accurate measurements of the QT intervals possible. The results in leads I and II were essentially similar, for simplicity, only the results of lead II are presented.

In general, the degree of electrocardiographic response to a single dose of one of the cinchona derivatives followed a characteristic curve (chart 2). The effect became evident shortly after the administration of the drug and increased rapidly, reaching a maximum in one and one-half to three hours. Thereafter, the degree of effect was maintained at a slightly lower level for approximately three to five hours,

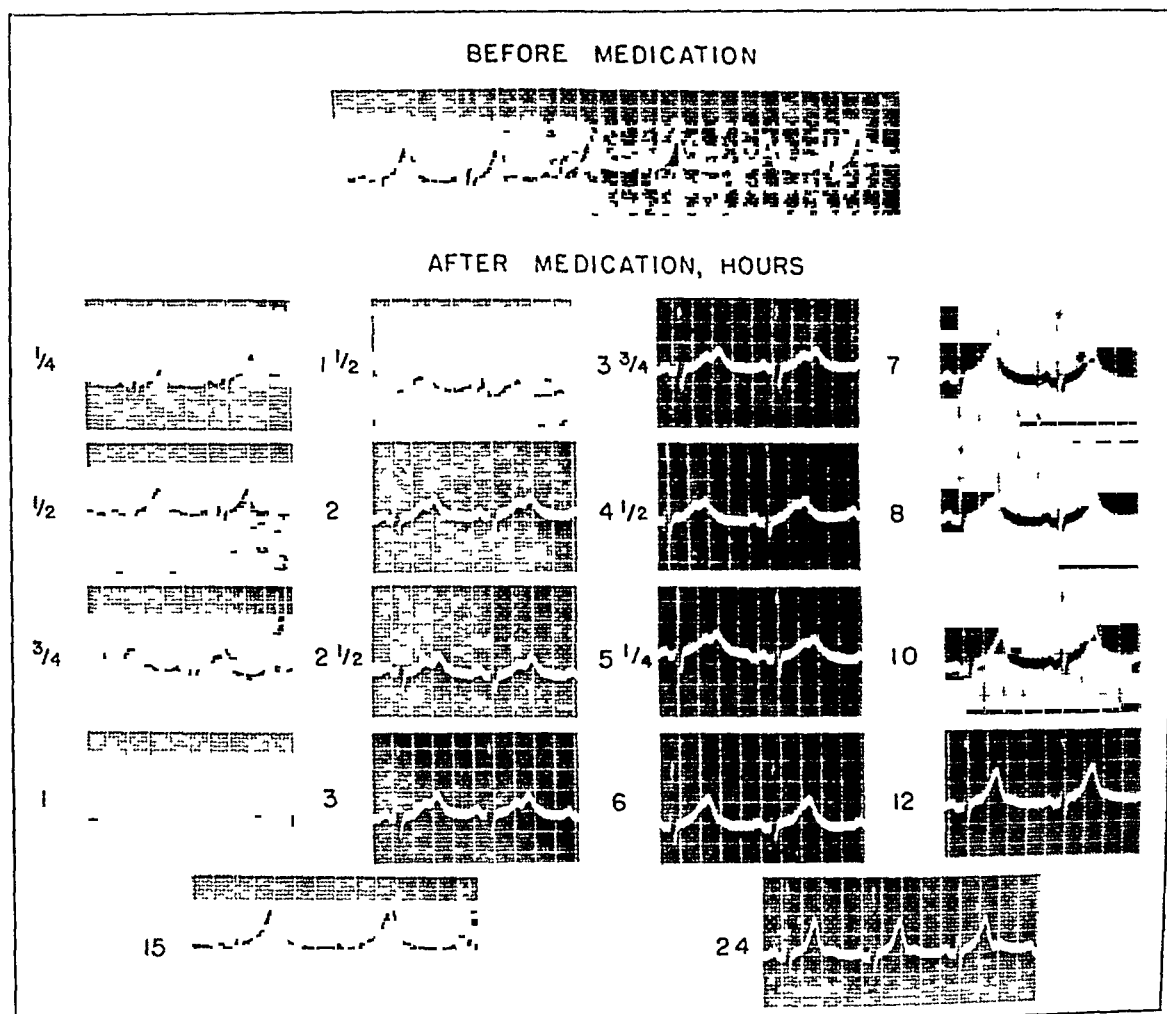


Fig 1—Typical prolongation of the QT interval and flattening of the T waves in the electrocardiogram following the administration of quinine (patient N J, 15 grains of quinine sulfate by mouth, lead IVr)

after which it decreased, at first rapidly and then more slowly, and was no longer evident in twenty-four hours.

*The Effect of Single Doses*—The Comparative Effects of Different Amounts of Quinine Sulfate Given Orally in Single Doses. These were studied in 14 patients. Eleven patients received 3 grains, 10 received 5 grains (0.3 Gm), 3 received 9 grains (0.6 Gm), 6 received 10 grains and 6 received 15 grains. The comparative effects of these different doses is best shown by the results obtained in 6 patients, each of whom received 3, 5, 10 and 15 grains on different days (chart 3).

The Comparative Effects of Oral and Intramuscular Administration of Quinidine Six of the patients who were given single 5 grain doses of quinidine sulfate by mouth subsequently received 5 grains of injectable quinidine (quinidine hydrochloride with urea and antipyrine) by the intramuscular route (chart 4) All patients showed a definite response within fifteen minutes, tracings for 2 patients were obtained five minutes after the injection and showed the characteristic effect In comparison, 4 of these 6 patients after a similar dose by mouth failed to show electrocardiographic changes until one to one and one-half hours The maximum effect of the intramuscular injection was obtained in one and one-half hours in all

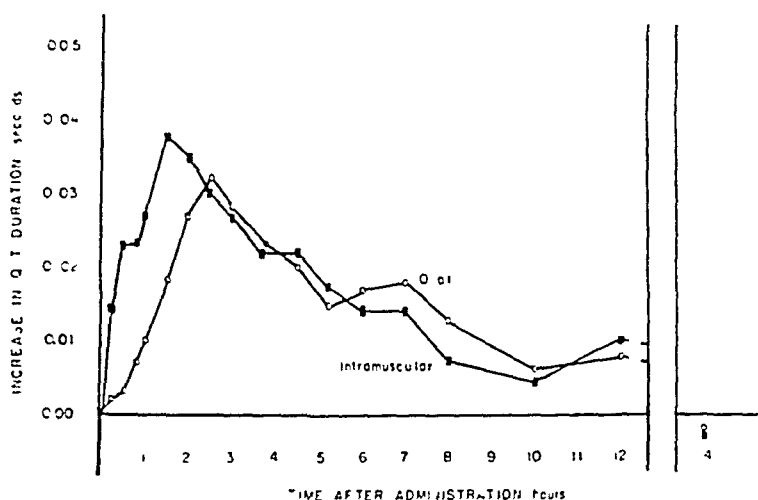


Fig 4—The comparative effects of oral and intramuscular administration of quinidine (average of results obtained in 6 patients)

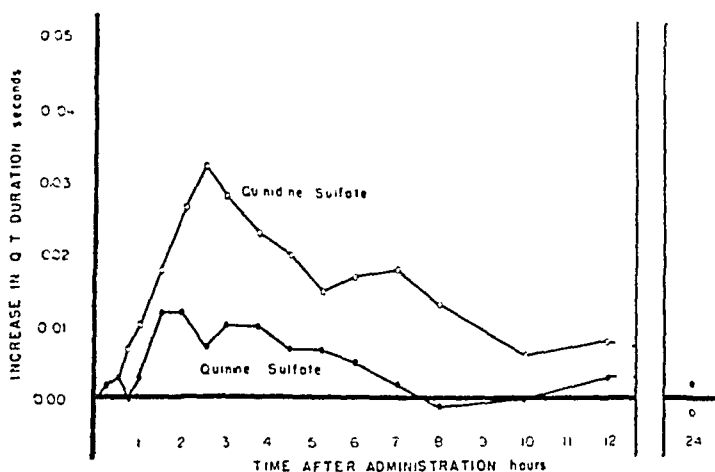


Fig 5—The comparative effects of quinidine sulfate and quinine sulfate (average of results obtained in 6 patients)

6 patients, whereas when the drug was given orally 5 failed to show the maximum effect until two to two and one-half hours In 4 patients the maximum effect following intramuscular injection was significantly greater than that following oral administration The duration of the effect was approximately the same when the drug was given by the two different routes

Comparison of Quinidine Sulfate and Quinine Sulfate The same 6 patients were given 5 grain doses of quinine sulfate by mouth (chart 5) Although similar electrocardiographic changes were observed in response to quinine sulfate, the magnitude and duration of these changes were much less than those following administration of quinidine sulfate

TABLE 1—*Variation in Response to Single Doses of Quinidine Following Oral and Intramuscular Administration*

Patient	Onset of Recognizable Effect (Hours After Administration)						Maximum Effect (Hours After Administration)						Disappearance of Effect (Hours After Administration)					
	Oral						Oral						Oral					
	3 Gr	5 Gr	10 Gr	15 Gr	I M 5 Gr		3 Gr	5 Gr	10 Gr	15 Gr	I M 5 Gr		3 Gr	5 Gr	10 Gr	15 Gr	I M 5 Gr	
I L	1	1/4	1/4	1/4	1/4	1/4	1 1/2	1 1/2	2	1 1/2	1 1/2	1 1/2	8 10	8 10	>8	>15	>10	>10
B K	1/4	1	1	1/4	1/4	1/4	2 2 1/2	2	2	2 1/2	1 1/2	2	8 10	8 10	>12	>15	7 8	7 8
I S	1 1/2	1 1/2	1/4	1	1/4	1/4	2 1/2	2	2	2 1/2	1 1/2	2	8-10	>12	>12	>15	>10	>10
II J	1	1 1/2	1/4	1/4	1/4	1/4	2 1/2	2 1/2	2 1/2	3 1/4	1 1/2	2	10	10-12	8 10	>15	8 10	8 10
E H	1	1/2	1/4	1/4	1/4	1/4	2	2 1/2	2 1/2	2 1/4	1 1/2	2 1/2	>12	>12	>12	>15	7 8	7 8
E B	1/2	1 1/2	1/4	1	1/4	1/4	1 1/2	2 1/2	2 1/2	2 1/2	1 1/2	2 1/2	>12	>12	>12	>15	7 8	7 8
H R	1						3						7					
J Z	3/4						2 3						6					
M T	1/2						1 1/2						6					
S G	1/2						1 1/2						8					
G B	1/2						1 2						8					
J W		1/2						2 2 1/2						>10				
O G		1/4						1 1/2						>10				
M S		1/2						1 1/2						8 10				
M R		1/2						2						>8				
Average	1/4	1/4	1/2	1/2	1/4	1/4	2	2 1/2	2 1/2	2 1/2	2	2	8-10	8 12	>12	>15	7 10	7 10

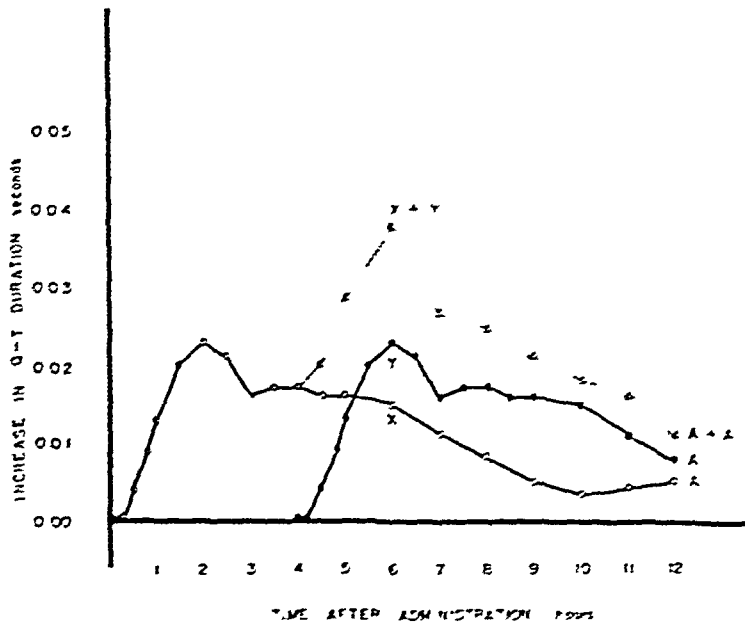


Fig 6—Method of calculating response to repeated doses. Curve *A* indicates response to a single 3 gram dose of quinidine sulfate given by mouth (average of results obtained in 11 patients). Curve *A'*, similar results which would have been obtained if a previous dose had not been given. Curve *AA'*, predicted effect of repeated doses obtained by the addition of curves *A* and *A'*.

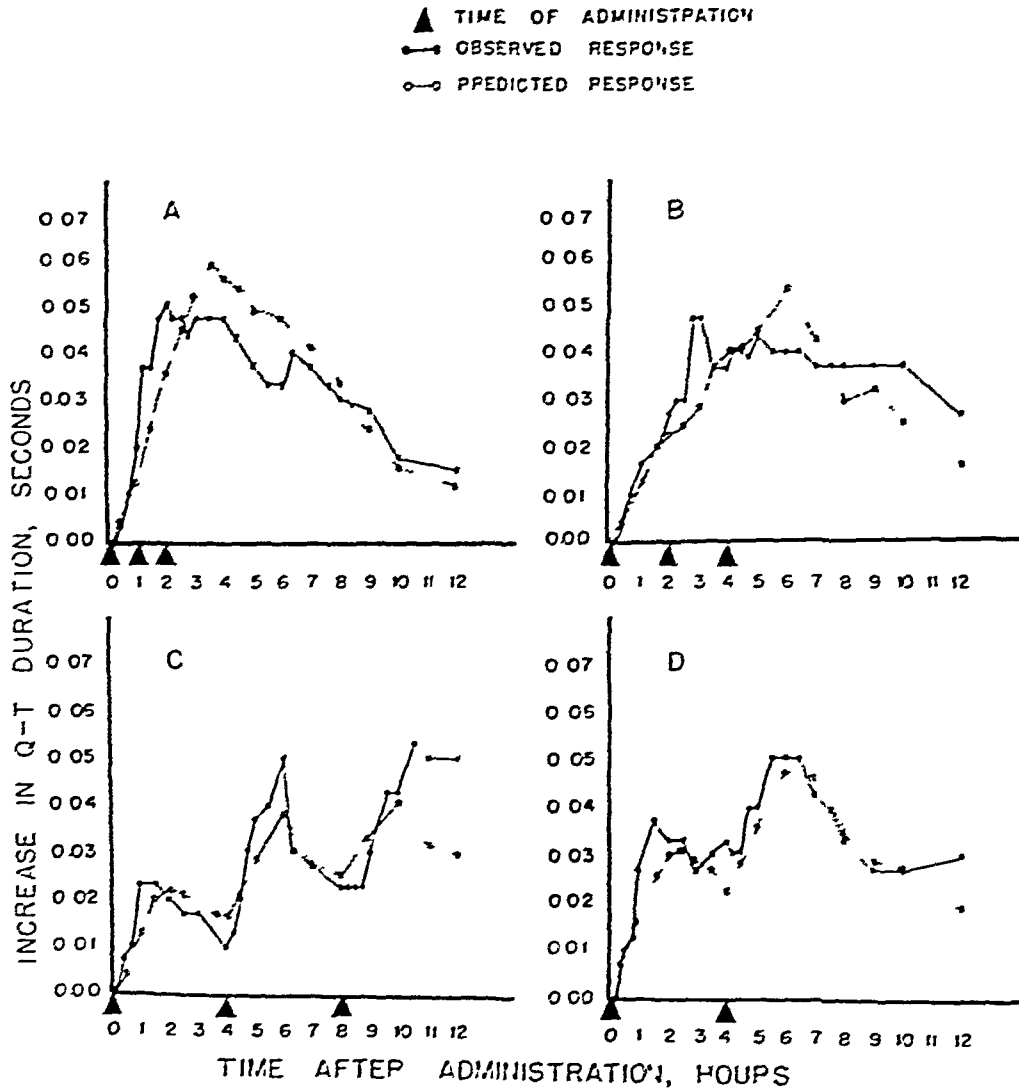


Fig 7—Comparison of the observed and the predicted response to repeated oral doses of quinidine sulfate. *A*, 3 grains at hourly intervals for three doses. *B*, 3 grains at two hour intervals for three doses. *C*, 3 grains at four hour intervals for three doses. *D*, 5 grains at four hour intervals for two doses. The observed response is an average of results obtained in 3 patients, the predicted response is based on an average of results obtained in 11 patients (*A*, *B* and *C*) and 9 patients (*D*).

*The Effect of Repeated Doses*—The Effect of Repeated Doses of Quinidine Sulfate Given Orally This was studied in 9 patients (table 2) The effect of medication administered repeatedly in this manner was compared with the response to single doses of 3 or 5 grains and also with the response to single doses equal in magnitude to the total amount given, namely, 9, 10 and 15 grains

Comparison of the Effects of Single and Repeated Three and Five Grain Doses In general, the effect of repeated doses could be predicted from the response to a single dose The effect of repeated doses at any time was approximately the sum of the effects of the individual doses administered up to that moment as known from previous curves of the responses to single doses The method of predicting the combined effects from the individual curves is shown in chart 6

When medication was administered at hourly intervals, the patient received successive doses before the maximum effect of the preceding dose had been obtained As a result the effect increased progressively, reaching a maximum two to four hours after the first dose (chart 7 *A*) The effect did not disappear entirely twelve hours after the first dose was given (ten hours after the third dose)

When medication was administered at two hour intervals, the patients received successive doses shortly after the maximum effect of the preceding dose had been

TABLE 2—*Dosage Used for Study of Effect of Repeated Oral Administration of Quinidine Sulfate*

Size of Dose, Grains	Hours Between Administration	Number of Doses	Number of Patients Studied
3	1	3	3
3	1	5	2
3	2	3	3
3	2	5	2
3	4	3	3
3	8	4	2
5	4	2	3

reached As a result it was usually possible to observe the maximum effect of each dose before the succeeding dose was administered (chart 8) When medication was administered at two hour intervals instead of at hourly intervals, the maximum prolongation of the QT interval began later and persisted longer but was approximately of the same magnitude (chart 7 *A* and *B*)

When medication was administered at four hour intervals, the effect of the preceding dose had decreased sufficiently so that the response to each individual dose was even more apparent than when the drug was given at two hour intervals (chart 7 *B*, *C* and *D* and chart 8) Here again the maximum prolongation of the QT interval was of approximately the same magnitude as when the same dose was given at more frequent intervals

When medication was administered at eight hour intervals, the effect of the preceding dose had practically disappeared As a result the response to the fourth dose administered was essentially the same as the response to the first dose in speed of onset, magnitude and duration (chart 9)

When medication was repeated five times (at either one or two hour intervals), the effects of the fourth and fifth doses were somewhat less than the effects of the individual first three doses

Comparison of the Effect of Nine, Ten and Fifteen Grains of Quinidine Sulfate Given in Single and Divided Doses When 9 or 10 grains was given in divided doses (3 or 5 grains given at one, two or four hour intervals for two or three

of the QT interval followed the administration of the drug by the intramuscular route. Regardless of the route of administration, when the drug was given at two hour intervals, it was usually possible to observe the maximum effect of the preceding dose.

#### COMMENT

It is evident from the literature that the magnitude of response to quinidine varies with the amount administered and that if repeated doses are given at appropriate intervals evidence of cumulative action becomes apparent. The concentration of cinchona derivatives in the blood, myocardium or urine after administration of the drug is of considerable interest, but these studies give little direct information concerning the degree and time of the therapeutic action in man.

More direct information of the clinical response is obtained from studies of the effect in various arrhythmias. As a result of such information many different methods of administering quinidine have been proposed. The drug has been prescribed in increasing or identical doses at periods varying from once an hour to once every five or six hours.<sup>17</sup> These methods have proved of value in treating chronic auricular fibrillation and in the prophylactic treatment of paroxysmal arrhythmias. They are obviously unsuited for the treatment of acute episodes for which rapid control of the rhythm may be necessary and for which it is advisable to evaluate the effect of previously administered medication before additional doses are given with the least possible delay.

Although the electrocardiographic changes following administration of quinidine have been previously recognized, few attempts have been made to utilize this knowledge for studying the effect of cinchona derivatives on the human heart. The results obtained in the present study show that although qualitative changes in the T wave as described by Maher, Sullivan and Scheribel<sup>10e</sup> may be striking, they vary in different patients and in the same patient at different times and may be absent or not sufficiently definite to make accurate measurement possible.

The prolongation of the QT interval following the administration of cinchona drugs in our experience is a constant factor which varies but little in different patients. This change is measurable and increases as the amount of drug is increased. It is probably closely related to the mechanism responsible for the conversion of abnormal to normal rhythm, for the QT interval (duration of electrical systole) is related to the refractory period of the ventricular muscle. In the treatment of ventricular tachycardia, for example, the quinidine effect is evidenced by a prolongation of the duration of each ventricular complex.<sup>9</sup>

The results of the present studies are in accord with the observations of the effect of quinidine made in the clinical treatment of arrhythmias. The present studies are more complete, however, for the response was observed for longer periods and under conditions which lent themselves to more careful quantitative measurement. That the results observed in normal subjects are applicable to patients with abnormal cardiac rhythms has been shown by clinical experience.<sup>18</sup>

The present studies show that the maximum effect of any single dose of quinidine or one of its derivatives is usually attained in one and one-half to two

17 (a) Weisman, S. A. The Ambulatory Treatment of Auricular Fibrillation with Quinidine. A Five-Year Follow-Up Study, *Minnesota Med* **19** 349, 1936. (b) Kerr, W. J. Use of Quinidine in Cardiac Irregularities, in Stroud, W. D. The Diagnosis and Treatment of Cardiovascular Disease, Philadelphia, F. A. Davis Company, 1940, p. 1195. (c) Weiss, S. The Treatment of Vertigo and Syncope, *J. A. M. A* **118** 529 (Feb. 14) 1942. (d) Weisman (footnotes 1a and 3). Lewis, Drury, Wedd and Iliescu.<sup>41</sup>

18 Sturnick, M., Riseman, J. E. F., and Sagall, E. L. Studies on the Action of Quinidine in Man. II. Intramuscular Administration of a Soluble Preparation of Quinidine in the Treatment of Acute Cardiac Arrhythmias, *J. A. M. A* **121** 921 (March 20) 1943.

doses), the maximum prolongation of the QT interval was essentially the same as when the total amount was given as one single dose. When 15 grains was given in divided doses, the maximum effect was slightly less than that following the single dose. In each case, however, the response to the single dose appeared more rapidly and was less prolonged.

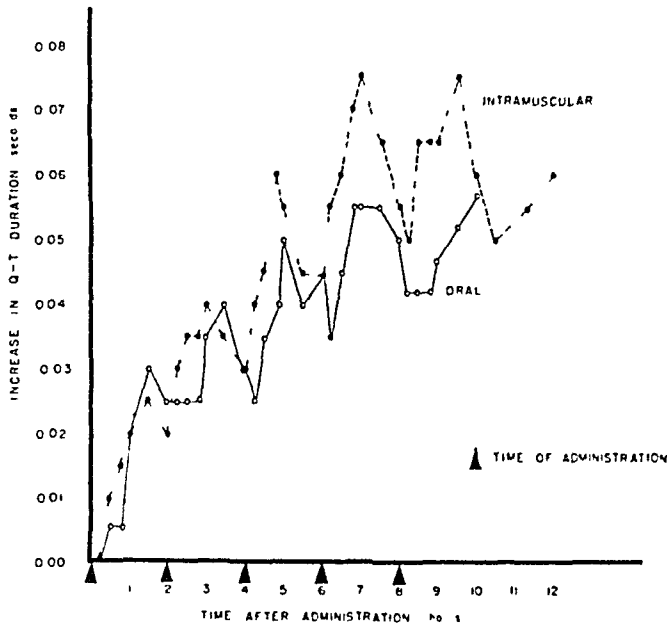


Fig 8—Comparison of the effects of repeated doses of oral and intramuscular preparations of quinine, 3 grains given at two hour intervals for five doses (average of results obtained in 2 patients)

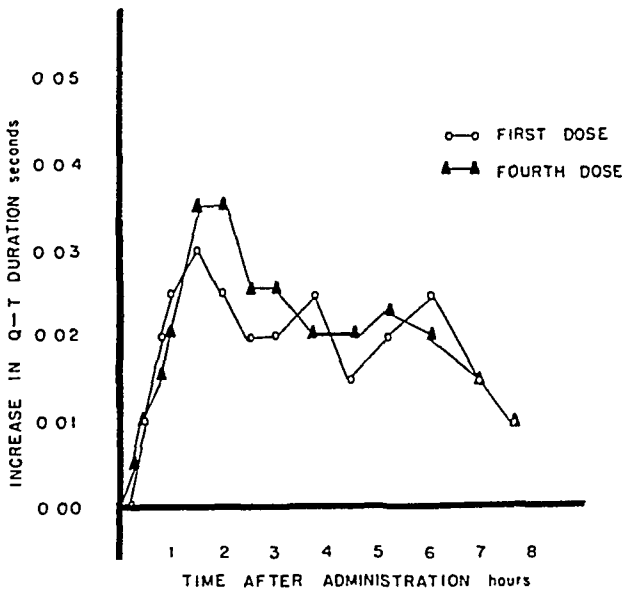


Fig 9—The effect of 3 grains of quinine sulfate administered by mouth at eight hour intervals. The electrocardiographic response to the first dose is compared to that of the fourth dose, which was given twenty-four hours later (average of results in 2 patients)

Comparison of the Effect of Repeated Doses of Oral and Intramuscular Preparations of Quinine. Two patients received five 3 grain doses of each preparation given at two hour intervals. The response to each intramuscular injection appeared within fifteen minutes, whereas the response to each oral administration did not appear for one-half to three-fourths hour. In most instances greater prolongation

the best of our knowledge the preparation used in this study for intramuscular injection has not been used heretofore in the treatment of cardiac arrhythmias. This preparation is not yet available commercially, but it can be prepared easily from drugs available now. Medication in such form can be carried in the physician's bag for emergency use and makes it possible to administer adequate quinidine dosage in small volumes. Administration by the intramuscular route is safe and not painful. Its use in the treatment of acute arrhythmias is being reported in a separate communication.<sup>18</sup>

#### SUMMARY AND CONCLUSIONS

After the administration of a cinchona derivative to a human being the electrocardiogram uniformly shows an increase in the time from the beginning of the Q to the end of the T wave. In the present study this index of the effect on the human heart was used to measure the speed and duration of action of quinidine and quinine administered to human beings either orally or by intramuscular injection.

The effect became evident shortly after the administration of a single dose by mouth, reached a maximum in one and one-half to three hours, was then maintained at a slightly lower degree for three to five hours, after which it decreased at first rapidly then more slowly, and was no longer evident in twenty-four hours.

Quinine was much less effective than quinidine.

Larger doses of quinidine sulfate did not change the time of the maximum response, although the effect became evident sooner and was more prolonged.

The response to intramuscular administration of injectable quinidine<sup>12</sup> (a solution of quinidine hydrochloride with urea and antipyrine) was much more prompt (within fifteen minutes) and the magnitude of effect was slightly greater, but the duration of effect was approximately the same as when an equivalent dose was given by mouth.

When doses are given repeatedly either orally or intramuscularly, the response at any moment is essentially the sum of the separate effects of the individual doses acting at that moment.

These results indicate that in the treatment of acute arrhythmias the administration of quinidine should be repeated at intervals of two to two and one-half hours. This permits observation of the maximum effect of the preceding dose before continuation of therapy with minimum loss of time.

If more rapid control of the rate is required, administration of the drug may be repeated at intervals of one hour until the desired degree of slowing is attained, after which therapy can be continued at intervals of two to two and one-half hours.

In the treatment of acute arrhythmias, intramuscular administration should provide more constant and earlier response and eliminate the uncertainties and irregular absorption of oral medication. Intravenous administration is unnecessary and unwise.

Mr. Harry Brass, Ph.G., assisted us in preparing the injectable quinidine.

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and one-half hours after administration. Obviously, therefore, *if the desired effect is not obtained within two hours additional quinidine will usually be necessary and delay in administering such medication is inadvisable*.

More rapid and more striking effects can be obtained by administering the drug at more frequent intervals, for example, every hour. Under such conditions the maximum effect of preceding doses will not have been obtained, and it is possible that toxic effects of quinidine may occur several hours after the drug is withdrawn. This method, however, is of value if the danger from continuation of the abnormal rhythm is greater than the danger from overquinidization.

It is probable that the toxic effects of quinidine have been overemphasized in the past. The untoward reactions may be grouped under four headings:

- 1 **Hypersensitivity.** This includes collapse with cardiorespiratory failure, etc. Such symptoms are likely to occur soon after the dose is administered and even after small doses. In the absence of a clearcut history of hypersensitivity to cinchona derivatives it is unlikely that such unfortunate complications can be avoided. In our experience with patients with angina pectoris<sup>19</sup> cutaneous manifestations of an allergic nature are likely to occur if quinidine has been administered previously, untoward reactions to quinidine, however, are uncommon. The infrequency of more serious reactions may possibly be related to the fact that quinine is less generally used as a therapeutic agent at present. The rarity of such reactions makes the danger of quinidine hypersensitivity much less than the danger of continuation of an acute arrhythmia in most instances.

- 2 **Reactions following conversion to normal rhythm.** These include embolic phenomena following resumption of normal auricular contractions in auricular fibrillation with dislodgment of mural thrombi. Sudden collapse with vomiting and marked fall in blood pressure following conversion to normal rhythm, even in the absence of embolic phenomena, is seen occasionally. Here again the reaction is not necessarily related to the size of the dose, and the possible danger from such effects must be weighed against the dangers of continuation of the abnormal rhythm.

- 3 **Reactions following overdosage.** These include vomiting, epigastric distress, diarrhea, fever and tinnitus. In most instances they can be avoided by giving no more quinidine than necessary to control the rate and rhythm.

- 4 **Precipitation of ventricular tachycardia or fibrillation.** Seven instances have been reported in the literature.<sup>20</sup> Five occurred during the treatment of auricular fibrillation, and the reaction was probably due to a slowing of the auricular rate without adequate auriculoventricular block. In the remaining 2 cases<sup>20d</sup> there were frequent attacks of ventricular fibrillation which occurred spontaneously or could be precipitated by several drugs, including quinidine given intravenously.

The advantages of intramuscular administration for the treatment of acute arrhythmias are obvious. The response to parenteral injection is prompt and quantitative. Furthermore, absorption is assured when the drug is administered by injection, while when given by mouth it may be vomited or may remain in the stomach mixed with undigested food and not be available to cardiac tissues. To

19 (a) Riseman, J. E. F., and Brown, M. G. *Medicinal Treatment of Angina Pectoris* Arch. Int. Med. **60** 100 (July) 1937. (b) Freedberg, Riseman and Spiegel.<sup>10b</sup>

20 (a) Levy, R. L. *The Clinical Toxicology of Quinidin*, J. A. M. A. **78** 1919 (Sept 30) 1922. (b) Kerr, W. J., and Bender, W. L. *Paroxysmal Ventricular Fibrillation with Cardiac Recovery in a Case of Auricular Fibrillation and Complete Heart Block While Under Quinidine Sulfate Therapy*, Heart **9** 269, 1922. (c) Davis, D., and Sprague, H. B. *Ventricular Fibrillation: Its Relation to Heart Block*, Am. Heart J. **4** 559, 1929. (d) Schwartz, S. P., and Jezer, A. *The Action of Quinine and Quinidine on Patients with Transient Ventricular Fibrillation*, *ibid* **9** 792, 1934.

in that the time required to see a light of fixed intensity is recorded rather than the specific intensities recognized at different time intervals during the dark adaptation period. At weekly and occasionally at biweekly intervals the vitamin A and carotene content of the fasting blood (taken by venipuncture) was determined according to the method of May,<sup>5</sup> 2 cc of serum being used rather than 1 cc. The blood values were expressed in  $L_{440}$  units of carotene and  $L_{625}$  units of vitamin A per hundred cubic centimeters of serum corrected for the blue color due to carotene. These values were converted into micrograms of carotene and U S P units of vitamin A respectively by use of the factors determined by Yarbrough and Dann.<sup>6</sup> Blood for total white blood cell counts and differential counts was taken from the ear each week. The counts were made on 200 cells.<sup>7</sup>

The material for microscopic study of the skin<sup>8</sup> was furnished by medium punch biopsy specimens taken from the lateral external portion of the thigh at four and seven month intervals of depletion. Since any thickening of the skin which might occur would decrease the visibility of the capillaries, they were examined with a capillary microscope applied to the cuticle area of the finger two or three times during the experimental period. During the last week of the experiment the eyes of each subject were examined with a slit lamp<sup>9</sup> and the findings recorded according to the system used by Kruse.<sup>10</sup> On the day preceding the termination of the experiment each subject was allowed a measured volume of 95 per cent alcohol (minimum 50 cc), which was taken with carbonated waters. The effect of the alcohol on the level of vitamin A in the blood was studied four and twelve hours respectively after the intake.

## RESULTS

*1 Dark Adaptation*—(a) Biophotometer. A comparison of the 20 to 30 second dial readings following bleaching of the 6 subjects with similar readings reported by Jeans<sup>11</sup> places 5 of the subjects in the borderline zone (19 to 24) and one in the subnormal zone (below 18). The deficiency diet had little effect on these readings. Although there were slight fluctuations in both directions, 1 e from borderline to normal and subnormal, the subjects maintained their relative groupings (fig 1).

(b) Adaptometer. The cone and rod thresholds for all subjects fell within the normal range reported by Hecht<sup>12</sup> (cone threshold 5.3 to 6.0 log units, rod threshold 2.7 to 3.0 log units). Throughout the entire period these thresholds remained constant for each subject, fluctuating only within the daily variation of 0.3 to 0.4 of a log unit for rod and cone thresholds respectively. In figure 2 are presented the cone and rod thresholds for every test on subject F W. The data for the other subjects show similar figures.

(c) Regonometer. The time necessary to see the five consecutive flashes of the first and second dot for the subjects was well within the normal time limit given by Blanchard,<sup>13</sup> namely, one and three minutes respectively.

5 May, C. D., Blackfan, K. D., McCleary, J. F., and Allen, F. H. Clinical Studies of Vitamin A in Infants and Children, *Am J Dis Child* **59** 1167-1184 (June) 1940.

6 Yarbrough, M. E., and Dann, W. J. Dark Adaptometer and Blood Vitamin A Measurements in a North Carolina Nutrition Survey, *J Nutrition* **22** 597-607 (Dec) 1941.

7 Helen Parkes Hunt took all the blood samples and did the blood counts.

8 Dr S. W. Becker examined the biopsy specimens which were taken in the Dermatology Clinic.

9 Dr A. C. Krause of the Ophthalmology Department examined the eyes.

10 Kruse, H. D. The Ocular Manifestations of Avitaminosis A, with Especial Consideration of the Detection of Early Changes by Biomicroscopy, *Pub Health Rep* **56** 1301-1324 (June 27) 1941.

11 Jeans, P. C., Blanchard, M. S., and Zentmire, Z. Dark Adaptation and Vitamin A, *J A M A* **108** 451-458 (Feb 6) 1937.

12 Hecht, S., and Mandelbaum, J. Relation Between Vitamin A and Dark Adaptation, *J A M A* **112** 1910-1916 (May 13) 1939.

13 Blanchard, E. L., and Harper, H. A. Measurement of Vitamin A Status of Young Adults by Dark Adaptation Technic, *Arch Int Med* **66** 661-669 (Sept) 1940.

# EFFECTS OF VITAMIN A DEPLETION IN YOUNG ADULTS

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The lack of agreement as to what constitutes subclinical vitamin A deficiency and the uncertainty existing as to the order of the occurrence of the supposed early signs in relation to one another prompted the undertaking of this study. The various suggested symptoms of early avitaminosis A include defective dark adaptation, macroscopic and microscopic changes in the skin and conjunctivas, changes in the total and differential white blood counts and decreased vitamin A content of the blood. Each of these factors has been investigated individually, there have been studies in which only two or three of the aforementioned signs have been followed in any one subject, the most usual method being to observe dark adaptation and one other sign. It was believed, therefore, that careful observations for all of the suggested subclinical signs of progressive vitamin A deficiency in the same subjects on a vitamin A-low diet would at least clarify the order of their appearance.

In conjunction with this investigation a study on animals<sup>1</sup> in which the hepatic stores of vitamin A of rats on a vitamin A-free diet were correlated with some of these same signs was also undertaken with the hope that it might furnish data to help interpret the findings in human subjects.

## EXPERIMENTAL METHODS

Six university students, 4 women and 2 men, ranging in age from 20 to 24 years, were placed on a vitamin A-low diet - for thirty-one and twenty weeks respectively. The diet contained from 67 to 100 U S P units of vitamin A per day. The foods furnishing any vitamin A or source thereof were weighed and consumed in equal amounts by all, with the exception of meat, of which the men received one and one-half times as much as the women. All other foods were allowed as desired. The flour used for cooking and baking was enriched. No concentrates were added to the diet, since it furnished adequate amounts of the other dietary constituents for a sedentary adult, according to the standards set up by the National Research Council. One of the women (subject S B) acted as the control and received 10,000 U S P units of vitamin A daily in the form of halibut liver oil capsules<sup>2</sup> in addition to the vitamin A-low diet.

The method employed for detecting the effects of vitamin A deficiency included measurements of dark adaptation and visual fields, of the vitamin A and carotene content of the blood and of histologic changes in the skin and conjunctivas. Total white blood cell counts and differential counts were also included. Most of these analyses were made prior to the experimental regimen, so that the normal base line for each subject could be determined. Dark adaptation was measured on three instruments. Two tests a week were given each subject, both on the biophotometer and on the Hecht adaptometer, during the last two or three weeks the subjects were tested on the regenometer,<sup>4</sup> which differs from the preceding two instruments.

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From the Department of Home Economics, the University of Chicago

1 Brenner, S, Brookes, M C H, and Roberts, L J. The Relation of Liver Stores to the Occurrence of Early Signs of Vitamin A Deficiency in the White Rat, *J Nutrition* **23** 459-471 (May) 1942

2 The skimmed milk was supplied by the Borden-Wieland Co, Chicago

3 The halibut liver oil capsules were furnished by Abbott Laboratories, North Chicago, Ill

4 The regenometer was sent by Dr Blanchard of the Golden State Co, Ltd, San Francisco

(d) Visual field The visual field did not seem to be impaired in any way as measured by perimetry

2 *Blood Carotene and Vitamin A*—The vitamin A and carotene content of the blood of all 6 subjects (table 1) prior to the experimental diet compared favorably with that reported by others using the same method<sup>14</sup> The carotene content of the blood at the outset (139 to 210 micrograms) varied with the dietary habits of the subjects This did not hold for vitamin A (87 to 150 U S P units) With the deficiency diet the blood carotene showed a steep and immediate drop in the first weeks, and then the rate of loss began to decrease until a plateau was reached Even at the end of the experiment the blood was not completely free of carotene (30 to 44 micrograms), but this is not to be expected since the vitamin A-low diet did contain small amounts of it The vitamin A content of the blood, on the other hand, with the exception of small fluctuations, remained at the original level for the duration of the depletion period Subject S B, who had the lowest level, continued to have a low level, of approximately 87 U S P units, in spite of the daily consumption of 10,000 units of the vitamin, while the other subjects on their decreased intake maintained higher levels (107 to 150 U S P units)

TABLE 1—*Carotene and Vitamin A Content per Hundred Cubic Centimeters of Serum Before and After Depletion*

Subject	Sex	Weight Pounds	Before Depletion		After Depletion	
			Carotene, Micrograms	Vitamin A, U S P Units	Carotene, Micrograms	Vitamin A, U S P Units
S B	Female	115	262	87	38	89
B G	Female	141	218	112	37	123
E S	Female	140	178	107	41	115
F W	Female	110	262	126	42	112
A A	Male	201	139	150	30	132
H O	Male	153	310	119	44	129

than that of the control subject At times several of the experimental subjects showed unusual rises in the vitamin A content of the blood

The level of vitamin A in the blood was extremely sensitive to colds and increased body temperature<sup>15</sup> During the fourth week of the experiment all the subjects, including the control, caught colds and had slight elevations in temperature The level of the vitamin in the blood reflected this condition by dropping to about one half of the initial value When the fever disappeared the vitamin A content of the blood resumed its normal level (fig 3)

Effect of Alcohol on Vitamin A Level of Blood Table 2 and figure 3 contain a summary of the effects of alcohol on the level of vitamin A in the blood of the women after thirty-one weeks and of the men after twenty weeks of deficiency Although 50 cc of alcohol was not a sufficient amount to cause any apparent rises in the vitamin A content of the blood of the experimental subjects, 75 to 100 cc caused a noticeable rise four hours after consumption After twelve hours the vitamin A

14 (a) Kimble, S M The Photoelectric Determination of Vitamin A and Carotene in Human Plasma, *J Lab & Clin Med* **24** 1055-1065 (July) 1939 (b) May<sup>5</sup> (c) Murrill, W A, Horton, P B, Lieberman, E, and Newburgh, L H Vitamin A and Carotene Metabolism in Diabetic and Normals, *J Clin Investigation* **20** 395-400 (July) 1941 (d) Yarbrough and Dann<sup>6</sup>

15 Clausen, S W, and McCoord, A B The Carotenoids and Vitamin A of the Blood, *J Pediat* **13** 635-650 (Nov) 1938 Thiele, W, and Scherff, I Blood Vitamin A Picture in Fever, *Klin Wchnschr* **18** 1275-1277 (Sept 23) 1939

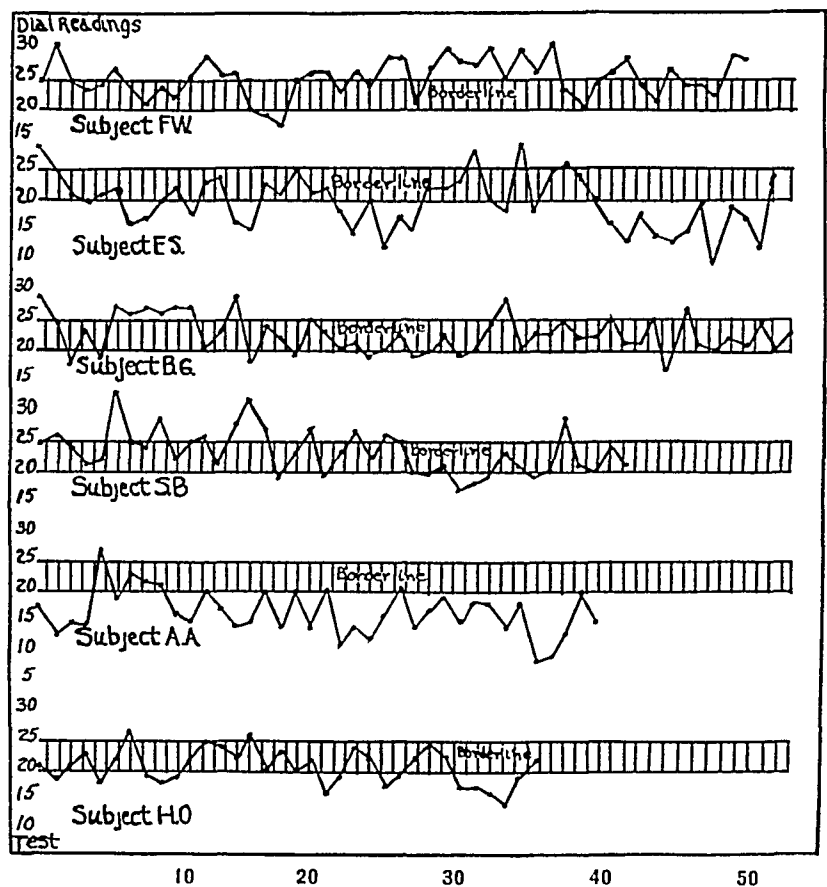


Fig 1—Individual biophotometer readings for first test after bleaching during deficiency period

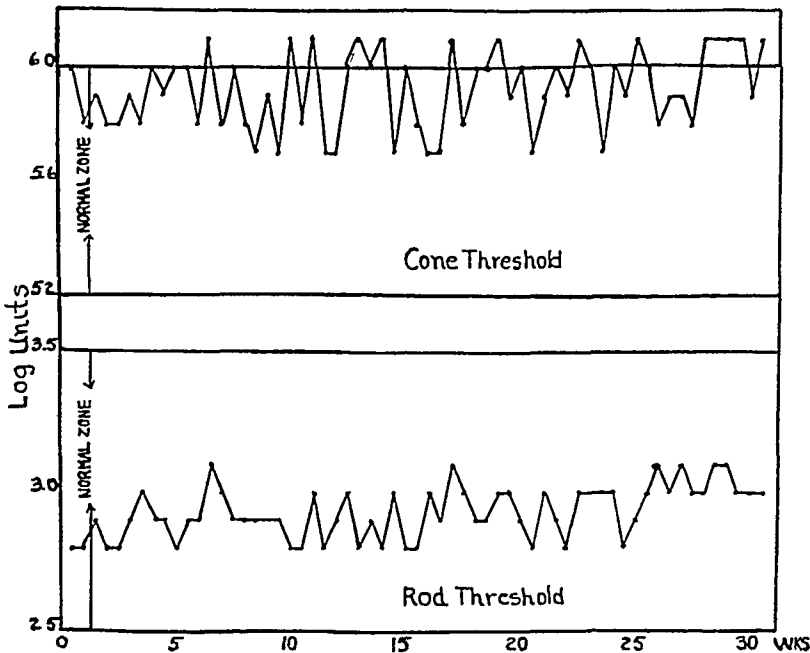


Fig 2—Cone and rod threshold for each test for subject F W Log units refer to intensities in micromicrolamberts

blood picture in relation to vitamin A, especially since these findings have not been confirmed in their entirety by others<sup>18</sup>

4 *Skin*—The biopsies made at four and seven month intervals of deficiency revealed no measurable differences in the subcutaneous structure of the hair follicles and sweat and sebaceous glands from that found prior to the experimental diet. The visibility of the capillaries remained as good as at the start, demonstrating that there was no keratinization of the epithelial tissue at the regions studied. The detailed findings of this portion of the study will be reported in another paper.

TABLE 2—*Effect of Alcohol on the Basal Level of Vitamin A in the Blood*

Subject	Alcohol, Cc	Vitamin A, U S P Units per 100 Cc Serum After Consumption of Alcohol		
		Basal	4 Hours	12 Hours
Control	50	139	157	136
	75*	142	151	163
E S	50	110	107	118
F W	50	112	125	127
B G	100	123	149	125
A A	100	132	181	149
H O	150*	129	155	125

\* The patient vomited one to one and a half hours after alcohol was taken

TABLE 3—*Average Total White Blood Cell and Differential Counts for Ten Week Periods of Depletion*

Subject	Depletion Time, Ten Week Intervals	Total White Cells	Poly morpho nuclears	Small Lympho cytes	Large Lympho cytes	Mono cytes	Eosino phils	Baso phils
S B	1st	6,033	111	64	4	18	3	1
	2d	5,978	115	60	5	15	3	1
	3d	5,670	117	53	8	19	2	1
B G	1st	10,260	102	78	4	11	5	0
	2d	10,390	96	85	4	9	7	0
	3d	10,310	105	71	9	10	7	1
E S	1st	9,360	110	71	5	12	2	0
	2d	7,760	103	75	4	9	3	0
	3d	7,217	105	74	7	11	4	1
F W	1st	8,620	112	70	4	12	2	0
	2d	8,430	106	78	4	9	2	0
	3d	8,300	114	65	8	9	2	1
A A	1st	9,100	98	86	5	9	2	1
	2d	8,022	97	87	6	8	2	1
H O	1st	8,800	121	63	3	11	2	1
	2d	7,745	103	79	5	11	2	1

5 *Examination of Eyes*—At the last week of deficiency there were no gross ocular signs. Mild photophobia was present in subjects E S and F W. Examination by slit lamp revealed a subconjunctival tissue slightly less translucent than normal in subjects E S and H O and a slight engorgement of the posterior conjunctival vessels in subjects B G and F W. The significance of these findings remains obscure, for similar examinations were not made prior to the experimental period. Since Bitot spots, conjunctival foam and changes in vascularity and translucency of the conjunctiva and cornea may occur in persons without vitamin A

18 Wagner, K. Early Symptoms of Vitamin A Deficiency in Man, *Klin Wchnsch* 19 567-568 (June 9) 1940

in the blood returned to its prealcoholic level in most instances. This would indicate that vitamin A was present in the bodies of the subjects after the depletion period and was capable of being mobilized by the alcohol, as was first demonstrated by Clausen and McCoord<sup>16</sup>

**3 Blood Picture**—According to the reports of Abbott and associates<sup>17</sup> the blood picture should be a valuable aid in the diagnosis of vitamin A deficiency because of the marked changes they obtained in rats and human beings on a vitamin A-low diet, namely, a decreased number of total white blood cells and polymorphonuclears or heterophils and an increased number of lymphocytes with the large lymphocytes predominating over the small. In addition, these authors found many juvenile and stab forms and degenerate cells.

None of the subjects in this study showed this type of picture (table 3). Several times some of the subjects did have a marked lymphocytosis (especially subject

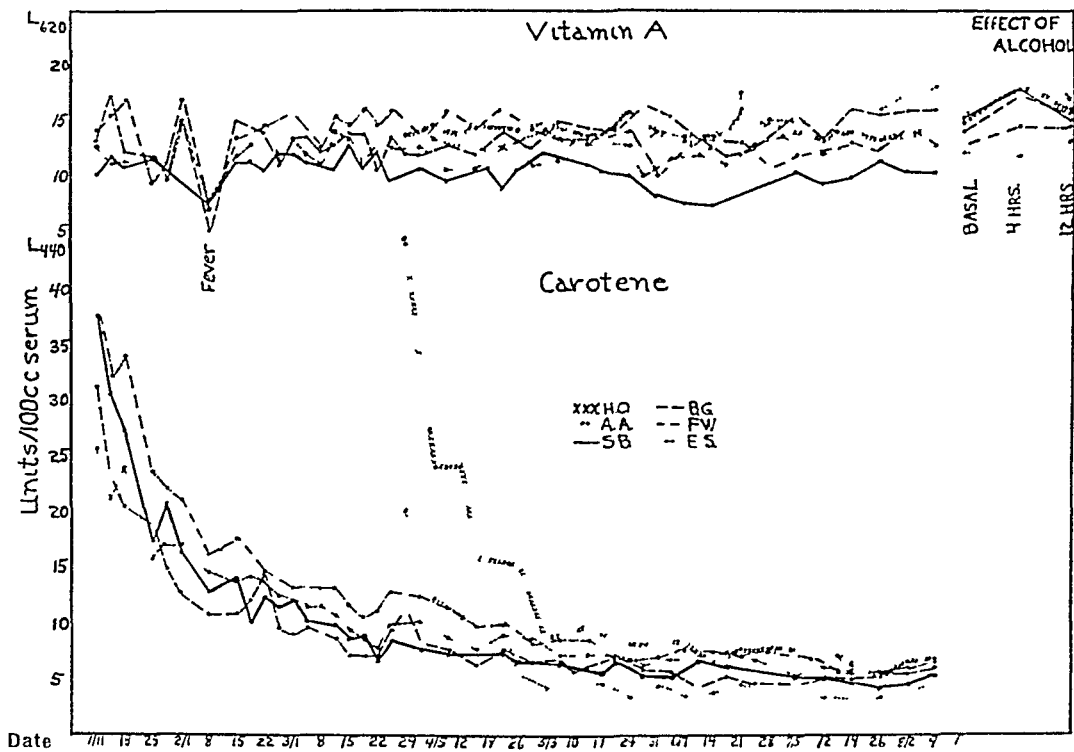


Fig 3—Vitamin A and carotene content of individual blood samples. L<sub>420</sub> units are corrected for blue color due to carotenoids. Subject S. B. was not the control for the alcohol study.

A. A.), but always the small lymphocytes predominated over the large and were in the main responsible for this condition. The polymorphonuclears were decreased at these times. Increased total white blood cell counts were not an accompaniment in every case, and at no time were there excess juvenile or degenerate cells. No infectious states were present to account for the increased number of lymphocytes. Further work is necessary to ascertain the significance of the change in

16 Clausen, S. W., Breese, B. B., Baum, W. S., McCoord, A. B., and Rydeen, J. O. Mobilization of Vitamin A from Its Stores in Tissues by Ethyl Alcohol. *Science* **91**: 318-319 (March 29) 1940. Effect of Alcohol on the Vitamin A Content of Blood in Human Subjects, *ibid* **93**: 21-22 (Jan. 3) 1941.

17 Abbott, O. D., and Ahmann, C. F. Effect of Avitaminosis A on the Blood Picture of Albino Rats, *Am. J. Physiol.* **122**: 587-595 (June) 1938. Abbott, O. D., Ahmann, C. F., and Overstreet, M. R. Effect of Avitaminosis A on the Human Blood Picture, *ibid* **126**: 254-260 (June) 1939.

was not ample. It is interesting to note that a theoretic calculation based on the average vitamin A content of human liver<sup>24</sup> and the assumption that the rate of use is approximately 2,000 U. S. P. units per day shows that it would take from one to two years for the liver to lose its entire vitamin A stores if no vitamin A were present in the diet.

The second explanation offered for the negative findings of this study is that these signs are neither sensitive nor specific for subclinical vitamin A deficiency. The contradictory evidence concerning their diagnostic value supports such a contention.

In respect to dark adaptation it has been shown that there is an inconsistency in the response of normal subjects to vitamin A-low diets in the various laboratories as well as in the response of deficient subjects to massive doses of vitamin A.<sup>25</sup> The specificity of night blindness as an indication of vitamin A deficiency has also been challenged by the curative effect of vitamin C and riboflavin in some cases.<sup>26</sup> There are indications, too, that several of the other symptoms may be more sensitive than dark adaptation as indicators of subclinical vitamin A deficiency.<sup>27</sup> This is quite conceivable, since animal experimentation reveals that the vitamin A content of the retina persists even in the absence of hepatic stores.<sup>28</sup>

Two additional alleged subclinical signs which have received a reasonable share of attention are the decreased vitamin A content of the blood and changes in the structure of the skin. The former has obtained support from the work of May,<sup>5</sup> Lewis, Bodansky and Haig<sup>27c</sup> and Yarbrough and Dann.<sup>6</sup> These investigators found the blood level the most sensitive indicator of vitamin A deficiency. On the other hand, Josephs<sup>22</sup> and Nylund<sup>23d</sup> with human beings and Brenner, Brookes and Roberts<sup>1</sup> with rats found that there is a wide range in the blood level of normal subjects and that only in prolonged and severe deficiency is the blood level valuable diagnostically. Changes in the skin, such as keratinization and resulting horny papules known as toadskin, have been reported by Lehman<sup>29</sup> in

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698-721 (Sept.) 1940 (c) Steffens, L. F., Bair, H. L., and Sheard, C. Photometric Measurements on Visual Adaptation in Normal Adults on Diets Deficient in Vitamin A, *Proc. Staff Meet., Mayo Clin.* **14** 698-704 (Nov.) 1940 (d) Nylund, C. E., and With, T. K. Demonstration of Vitamin A Deficiency in Man, *Acta med. Scandinav.* **106** 202-228, 1941 (e) Murrill, Horton, Lieberman and Newburgh<sup>14c</sup>

24 Abels, J. C., Gorham, A. T., Pack, G. T., and Rhoads, C. P. Metabolic Studies in Patients with Gastrointestinal Cancer. III. The Hepatic Concentration of Vitamin A, *Proc. Soc. Exper. Biol. & Med.* **48** 488-492 (Nov.) 1941

25 (a) Booher, L. E., Callison, E. E., and Hewston, E. M. An Experimental Determination of the Minimum Vitamin A Requirement of Normal Adults, *J. Nutrition* **17** 317-331 (April) 1939 (b) Wald, G., and Stevens, P. An Experiment in Human Vitamin A Deficiency, *Proc. Nat. Acad. Sc.* **25** 344-349 (Aug.) 1939 (c) Steininger, and Roberts<sup>23a</sup> (d) Isaacs, Jung and Ivy<sup>23b</sup> (e) Hecht, S., and Mandelbaum, J. Dark Adaptation and Experimental Human Vitamin A Deficiency, *Am. J. Physiol.* **130** 651-664 (Oct.) 1940 (f) Steffens, Bair and Sheard<sup>27c</sup> (g) Jeans, P. C., Blanchard, E. L., and Satterthwaite, F. E. Dark Adaptation and Vitamin A. Further Studies with the Biophotometer, *J. Pediat.* **18**. 170-194 (Feb.) 1941

26 Stewart, C. P. Nutritional Factors in Dark Adaptation, *Edinburgh M. J.* **48** 217-237 (April) 1941

27 (a) May, Blackfan, McCreary and Allen<sup>5</sup> (b) Steffens, Bair and Sheard<sup>27c</sup> (c) Lewis, J. M., Bodansky, O., and Haig, C. Level of Vitamin A in the Blood as an Index of Vitamin A Deficiency in Infants and Children, *Am. J. Dis. Child.* **62** 1129-1148 (Dec.) 1941 (d) Yarbrough and Dann<sup>6</sup>

28 Greenberg, R., and Popper, H. Demonstration of Vitamin A in the Retina by Fluorescence Microscopy, *Am. J. Physiol.* **134** 114-118 (Aug.) 1941 Brenner, Brookes and Roberts<sup>1</sup>

29 Lehman, E., and Rapaport, H. G. Cutaneous Manifestations of Vitamin A Deficiency in Children, *J. A. M. A.* **114** 386-393 (Feb. 3) 1940



deficiency as well as in those in all stages preceding severe vitamin A deficiency these signs are suggestive but not positive indications of deficiency

6 *Subjective Signs*—The general health of the subjects throughout the experiment was as usual. There were one or two colds during the winter, but this was no more than in previous years. There were no reports by the subjects of subjective night blindness. One (subject B G) complained of excessive fatigue which was most likely due to her heavy schedule and late hours.

#### COMMENT

It is seen, therefore, that normal, well fed adults did not present any of the alleged signs of subclinical vitamin A deficiency even after seven and one-half months on a depletion diet. Either or both of two factors may be responsible for such a result. Either the demand for vitamin A by the organism is not great enough to cause sufficient depletion of normal hepatic stores in seven and one-half months to result in the occurrence of the reported early signs of vitamin A deficiency, or these signs are not solely a result of uncomplicated vitamin A deficiency.

That an extensive degree of depletion of stores of vitamin A is a prerequisite for the development of the subclinical signs of deficiency is borne out by animal studies in which the occurrence of these signs has been correlated with liver stores by the greater prevalence of subclinical signs in children than in adults and in males than in females and by the relatively low incidence of defects in populations on vitamin A-meager diets. In rats it has been shown that a lag exists between the exhaustion of hepatic stores and the appearance of loss of weight and xerophthalmia.<sup>19</sup> In children and males the amount of vitamin A storage is less than in adults and females—in children because they have had less opportunity to acquire stores, in males (if a sex difference is accepted) because they store less and lose it more readily than females, as was shown in rats.<sup>20</sup> Steven's and Wald's investigation in Labrador<sup>21</sup> revealed only a small percentage of night blindness although to judge from the habitual dietaries a much greater percentage would have been expected. Josephs' <sup>22</sup> study of the vitamin A content of the blood and dark adaptation in various socioeconomic groups showed that only in severe and prolonged vitamin A deficiency were these measurements affected. The failure for as long as six months of controlled vitamin A-low diets to result in any of the specific signs of deficiency<sup>23</sup> is also indicative that the depletion period studied

19 Popper, H., and Greenberg, R. Visualization of Vitamin A in Rat Organs by Fluorescence Microscopy, *Arch Path* **32** 11-32 (July) 1941. Horton, P. B., Murrill, W. A., and Curtis, A. C. The Determination of Vitamin A in the Blood and Liver as an Index of Vitamin A Nutrition of the Rat, *J Clin Investigation* **20** 387-393 (July) 1941. Brenner, Brookes and Roberts.<sup>1</sup>

20 Bult, A. R., and Sorgdrager, C. J. Influence of Sex and Castration in Male Rats upon Vitamin A Metabolism, *Chem Abstr* **38** 775 (Feb 10) 1941. Brenner, Brookes and Roberts.<sup>1</sup>

21 Steven, D., and Wald, G. Vitamin A Deficiency. Field Study in Newfoundland and Labrador, *J Nutrition* **21** 461-476 (May) 1941.

22 Josephs, H. W., Baber, M., and Conn, H. Studies in Vitamin A. The Relation of Blood Level and Adaptation to Dim Light to Diet, *Bull Johns Hopkins Hosp* **68** 375-387 (May) 1941.

23 (a) Steininger, G., and Roberts, L. J. Biophotometer Test as Index of Nutritional Status for Vitamin A, *Arch Int Med* **64** 1170-1186 (Dec.) 1939. (b) Isaacs, B. C. Jung, F. T., and Ivy, A. C. Clinical Studies of Vitamin A Deficiency, *Arch Ophth* **24**

# EXCRETION OF COPROPORPHYRIN IN HEPATIC DISEASE

## IV ISOLATION AND IDENTIFICATION OF URINARY COPROPORPHYRIN ISOMERS

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Protoporphyrin III constitutes the prosthetic group of certain vital substances notably hemoglobin<sup>1</sup>. Only porphyrins of isomeric series I and III occur naturally in plants and animals, and Fischer<sup>2</sup> pointed out that it is inconceivable for porphyrins of types I and III to be transformed one to the other in any biologic process, that they must be formed individually in the physiologic synthesis. Porphyrin arises in the body during synthesis of hemoglobin rather than during its destruction, as had been supposed formerly a small proportion of isomeric series I arising as a by-product of the main synthesis of isomeric series III intended for utilization in the manufacture of hemoglobin<sup>3</sup>. The porphyrin of isomeric series I is not utilized and is excreted as coproporphyrin I, and any porphyrin of isomeric series III which has been synthesized in greater amounts than are necessary to meet the immediate requirements, or which is prevented from entering into the synthesis of hemoglobin by a toxic block, such as occurs with lead poisoning, is excreted as coproporphyrin III. Thus both coproporphyrins I and III might occur in the normal urine as well as pathologically. It was supposed formerly<sup>4</sup> that only coproporphyrin I was excreted normally in the urine until

Abstract of portion of thesis submitted to the faculty of the Graduate School of the University of Minnesota in partial fulfillment of the requirements for the degree of Doctor of Philosophy in Medicine

1 Best, C H, and Taylor, N B. The Physiological Basis of Medical Practice. A University of Toronto Text in Applied Physiology, ed 2, Baltimore, Williams & Wilkins Company, 1939. Carrie, C. Die Porphyrine. Ihr Nachweis, ihre Physiologie und Klinik, Leipzig, Georg Thieme, 1936. Mason, V R, Courville, C B, and Ziskind, E. The Porphyrins in Human Disease, *Medicine* **12** 355-439 (Dec) 1933. Morhardt, P E. Les porphyrines et leur rôle physio-pathologique, *Presse med* **2** 1200-1202 (Aug 12) 1931. Vannotti, A. Porphyrine und Porphyrinkrankheiten, Berlin, Julius Springer, 1937.

2 Fischer, H. Hämmin, Bilrubin und Porphyrine, *Naturwissenschaften* **18** 1026-1037 (Nov 28) 1930, Ueber Blut, Blatt und Gallenfarbstoff, in Oppenheimer, C. Handbuch der Biochemie des Menschen und der Tiere, ed 2, Jena, Gustav Fischer, 1930, supp, p 72, Ueber Hämmin und Porphyrine, *Verhandl d deutsch Gesellsch f inn Med* **45** 7-27, 1933.

3 (a) Dobriner, K. Porphyrin Excretion in Feces in Normal and Pathological Conditions, *J Biol Chem* **120** 115-127 (Aug) 1937. (b) Dobriner, K, and Rhoads, C P. The Metabolism of Blood Pigments in Pernicious Anemia, *J Clin Investigation* **17** 95-103 (Jan) 1938. (c) Dobriner, K. Strain, W H. Localio, S A, Keutmann, H, and Stephens, D I. II Coproporphyrin I Metabolism and Hematopoietic Activity, *Proc Soc Exper Biol & Med* **36** 755-756 (June) 1937. (d) Rimington, C. Porphyrins and Their Relation to the Metabolism of Blood Pigments, *Proc Roy Soc Med* **32** 1268-1275 (Aug) 1939. (e) Lemberg, R. Transformation of Haemins into Bile Pigments, *Biochem J* **29** 1322-1336 (June) 1935.

4 (a) Fink, H, and Hoerbuerger, W. Isolierung von kristallisiertem Koproporphyrin I aus normalem menschlichem Urin, *Naturwissenschaften* **22** 292 (April 27) 1934. (b) Watson, C J. Concerning the Naturally Occurring Porphyrins. IV The Urinary Porphyrin in Lead Poisoning as Contrasted with that Excreted Normally and in Other Diseases, *J Clin Investigation* **15** 327-334 (May) 1936.

children on relief and by Steffens, Ban and Sheard<sup>30</sup> in an adult maintained on a vitamin A-low diet for one hundred and eighty days. This condition has been described as occurring in scurvy, pellagra and other deficiency diseases,<sup>30</sup> the more severely affected patients being from the Orient, where the diet is totally inadequate in all the dietary constituents.<sup>31</sup> Since the deficiencies are multiple, the assumption that the lack of vitamin A alone is responsible for the cutaneous changes is not justified, even though massive doses of vitamin A have been effective in causing a cure, for in general other concentrates are also administered.

Moore<sup>30c</sup> in summing up the allowable claims for vitamin A deficiency stated

If, therefore, the claim that phrynoderma (toadskin) is acceptable as a manifestation of vitamin A deficiency, it is difficult to understand how night blindness can be accepted as an early or invariable symptom of vitamin A deficiency. But is phrynoderma due to a deficiency of vitamin A? There are a number of observers who hold it is not so.

From these existing uncertainties it is evident that much work needs yet to be done on the metabolism of vitamin A to elucidate the confusing evidence.

#### SUMMARY

Five young adults, 3 women and 2 men were placed on a vitamin A-low diet for seven and one-half and four and one-half months respectively. At suitable intervals measurements were made of dark adaptation, blood vitamin A and carotene, total white blood cell counts and differential blood counts and changes in the structure of skin and conjunctivas. None of these measurements showed any definite changes from those found prior to the deficiency for the length of time studied. It appears then either that these subjects had sufficient stores to withstand the effects of the depletion diet or that these signs are not merely the result of uncomplicated vitamin A deficiency.

Dis Becker, Krause and Oldham and Mrs Helen Parks Hunt gave cooperation in the work on this problem.

30 (a) Scheer, M., and Keil, H. Follicular Lesions in Vitamin A and C Deficiency, *Arch Dermat & Syph* **30** 177-185 (Aug.) 1934. (b) Keil, H. The Follicular Lesions of Vitamin A and C Deficiency. A Critical Survey, *Am J Digest Dis* **5** 40-48 (March) 1938. (c) Moore, F. D. Allowable Claims for Vitamin A Deficiency. The Relation of Visual Defect and Skin Lesions, *J Trop Med & Hyg* **44** 47-48 (April 15) 1941.

31 Frazier, C. N., and Hu, C. K. Nature and Distribution According to Age of Cutaneous Manifestations of Vitamin A Deficiency, *Arch Dermat & Syph* **33** 825-852 (May) 1938.

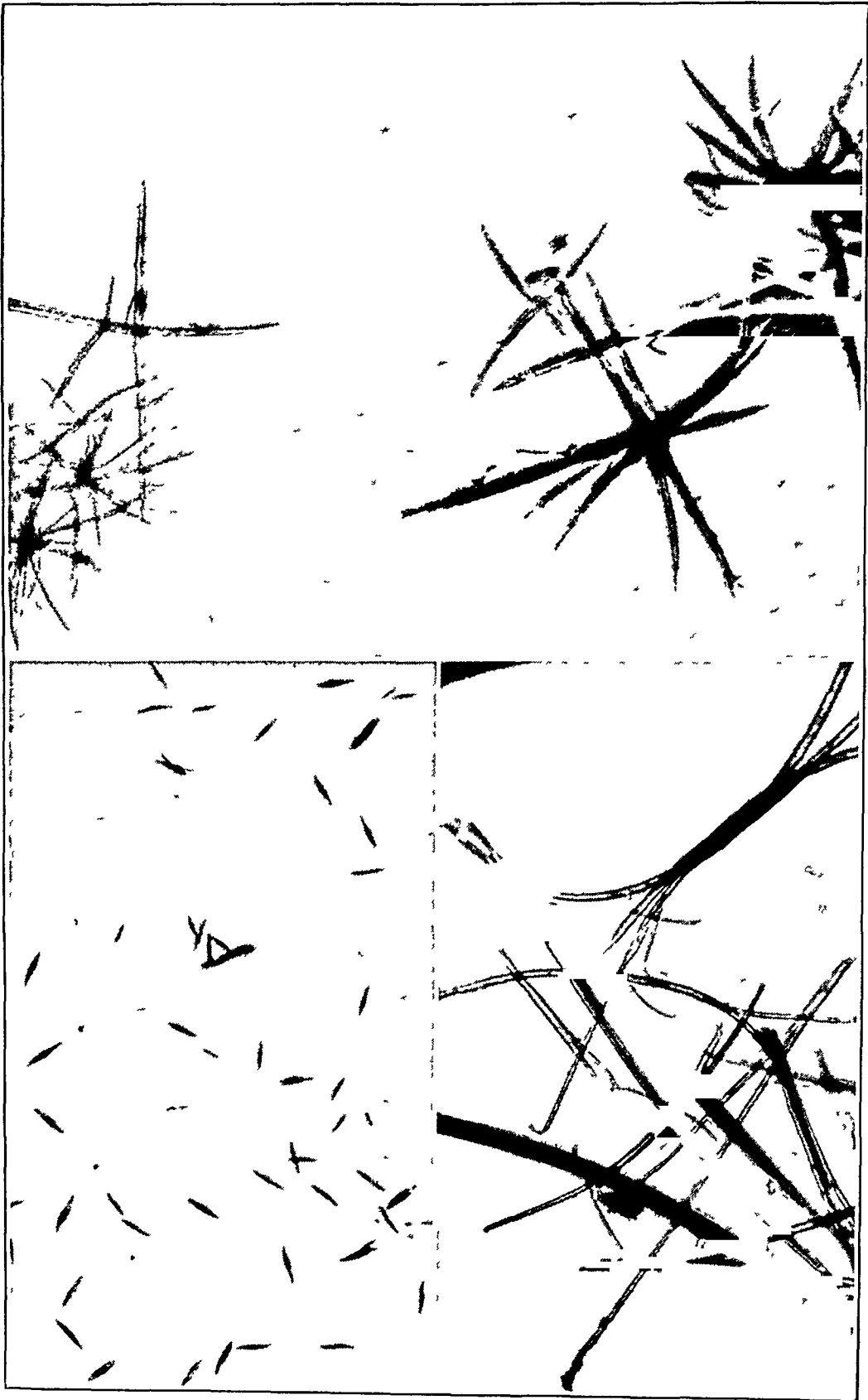


Fig 1—Crystals of coproporphyrin I methyl ester ( $\times 800$ )

Grotepass<sup>5</sup> isolated both coproporphyrin I and III from the urine of healthy persons. Since a possibility still exists that hemoglobin in the diet may afford an exogenous source of coproporphyrin III in the urine, Watson<sup>6</sup> suggested that a study similar to that of Grotepass, but carried out on the urine of subjects on a meat-free diet, would be of extreme importance.

The coproporphyrin is excreted by the liver and kidneys, the ratio of urinary excretion to fecal excretion depending chiefly on the patency of the bile passage and the efficiency of the liver, which is the more important organ of excretion. Normally only a small fraction of the total coproporphyrin excreted appears in the urine,<sup>7</sup> but this fraction is increased in the event of biliary obstruction or parenchymatous hepatic damage, a mechanism similar, indeed, to the excretion of bile pigments.

Reports have varied in those instances of hepatic disease in which the urinary coproporphyrin has been isolated and the isomeric type identified. The question arises whether the findings have been representative of hepatic damage or biliary obstruction in general, or whether they are related to some complicating circumstance in the particular cases investigated. Coproporphyrin I has been isolated from the urine of 20 patients suffering from such diseases as cinchophen cirrhosis, atrophic cirrhosis, hemolytic icterus, biliary obstruction, chronic passive congestion, lymphosarcoma of the liver, Hodgkin's disease involving the bile passage and catarrhal or infectious jaundice.<sup>8</sup> Coproporphyrin III has been isolated in 4 instances, including 1 case each of melanosis of the liver and hemochromatosis and 2 cases of atrophic cirrhosis.<sup>9</sup> The patient in one of the 2 latter cases had been receiving mercury for the treatment of syphilis, and because of this complicating toxic factor perhaps this case should not be included.

The present investigation represents the study of 10 patients who had various diseases of the liver or bile ducts, including carcinoma of the common bile duct, carcinoma of the head of the pancreas with biliary obstruction, obstructive biliary cirrhosis due to stone in the common duct, syphilitic hepatitis plus biliary cirrhosis due to stone in the common duct, hepatic metastasis from carcinoma of the rectum, subacute atrophy of the liver, atrophic cirrhosis and alcoholic cirrhosis. All these

5 Grotepass, W. Zur Kenntnis der natürlichen Harnporphyrine, *Ztschr f physiol Chem* **253** 276-280, 1938.

6 Watson, C. J. Porphyrins and Diseases of Blood, in a Symposium on Blood and Blood-Forming Organs, Madison, University of Wisconsin Press, 1939, pp 14-30.

7 Dobriner, K., and Rhoads, C. P. The Quantitative Determination of Urinary Coproporphyrin, *New England J Med* **219** 1027-1029 (Dec 29) 1938. Watson, C. J. Concerning the Naturally Occurring Porphyrins. I The Isolation of Coproporphyrin I from the Urine in a Case of Cinchophen Cirrhosis, *J Clin Investigation* **14** 106-109 (Jan) 1935. Nesbitt, S., and Snell, A. M. The Excretion of Coproporphyrin in Hepatic Disease. I Urinary and Fecal Excretion as Correlated with Parenchymatous Hepatic Damage, *Arch Int Med* **69** 573-581 (April) 1942. The Excretion of Coproporphyrin in Hepatic Disease. II Urinary and Fecal Excretion in Biliary Obstruction, *ibid* **69** 582-588 (April) 1942. Dobriner<sup>3a</sup> Watson<sup>4b</sup>.

8 (a) Dobriner, K. Urinary Porphyrin in Disease, *J Biol Chem* **113** 1-10 (Feb) 1936. (b) Dobriner, K., and Rhoads, C. P. The Porphyrins in Health and Disease, *Physiol Rev* **20** 416-468 (July) 1940. (c) Tropp, C., and Penew, L. Quantitative klinische Harnporphyrinuntersuchungen. II Mitteilung Lebercirrhosen, Hepatopathien (ausser Cirrhosen), Tuberkulose und andere Krankheiten, *Deutsches Arch f klin Med* **180** 411-422, 1937. (d) Vigliani, E. C., and Libowitzky, H. Ueber Porphyrine im Harn und im Kot, *Klin Wchnschr* **16** 1243-1245 (Sept 4) 1937. (e) Watson, C. J. Concerning the Naturally Occurring Porphyrins. II The Isolation of a Hitherto Undescribed Porphyrin Occurring with an Increased Amount of Coproporphyrin I in the Feces of a Case of Familial Hemolytic Jaundice, *J Clin Investigation* **14** 110-115 (Jan) 1935.

9 Dobriner<sup>3a</sup> Vigliani and Libowitzky<sup>8d</sup>

micrographs of crystals of coproporphyrin III. Study of the crystalline structure is interesting but is too unreliable to be of any great assistance. Table 1 represents the melting points of the coproporphyrin isomers I and III, as reported by various investigators.

The results of the present investigation are shown in table 2. In cases 1 and 2 the patients had obstructive jaundice, and coproporphyrins I and III were obtained.

TABLE 1—*Melting Points of the Methyl Esters of Coproporphyrins I and III in Degrees Centigrade*

References	Coproporphyrin I	Coproporphyrin III *	
Dobrinet <sup>14</sup>	252	142	172
Chandler, F. G., Harrison, G. A., and Rimington, C. Brit. M. J. <b>2</b> 1173, 1939	252	145	172
Fischer, H., and Neumann, F. W. in Luck, J. M. Annual Review of Biochemistry, Stanford University, Calif., Stanford University Press, 1932, vol. 1, pp. 527-534. Fischer, H., and Hiernis, J. Ztschr. f. physiol. Chem. <b>196</b> 155, 1931	250	145	165
Rimington, C. Lancet <b>1</b> 770, 1938, Onderstepoort J. Vet. Sc. <b>7</b> 567, 1936	245	144-146	169-172

\* Coproporphyrin III possesses a double melting point in that it may first melt at the lower temperature and after cooling melt at the higher temperature.

TABLE 2—*Presentation of Cases and Certain Data*

Case	Diagnosis	Range of Urinary Coproporphyrin, Micrograms	Days Observed	Coproporphyrin Fraction as Isolated	Weight, Mg	Melting Point, Degrees C.
1	Carcinoma of common bile duct with complete obstruction	79-615	16	1 Coproporphyrin I 2 Coproporphyrin I 3 Coproporphyrin III	1.3 1.0 *	248 240 166
2	Carcinoma of head of pancreas with complete common duct obstruction	20-287	19	1 Coproporphyrin I 2 Coproporphyrin III 3 Coproporphyrin III	0.7 0.3 *	240 138 165
3	Obstructive biliary cirrhosis, common duct stone	50-178	21	1 Coproporphyrin I 2 Coproporphyrin I	0.1 *	245 215
4	Hepatitis (syphilis), biliary cirrhosis (common duct stone)	76-280	9	1 Coproporphyrin I 2 Coproporphyrin III	0.1 *	243 165
5	Hepatic metastasis from carcinoma of rectum	190-520	8	1 Coproporphyrin I 2 Coproporphyrin I	0.2 *	247 243
6	Subacute atrophy of liver	115-600	49	1 Coproporphyrin I 2 Coproporphyrin III 3 Coproporphyrin III	1.8 1.25 *	247 165 170
7	Atrophic cirrhosis of liver (unknown cause)	100-630	17	1 Coproporphyrin I 2 Coproporphyrin I 3 Coproporphyrin I	0.2 * *	243 236 234
8	Alcoholic cirrhosis	400-782	5	1 Coproporphyrin III 2 Coproporphyrin III	1.1 *	140 138
9	Alcoholic cirrhosis	100-600	93	1 Coproporphyrin I 2 Coproporphyrin I 3 Coproporphyrin III	4.0 1.2 1.0	243 240 167
10	Alcoholic cirrhosis	414-838	48	1 Coproporphyrin I 2 Coproporphyrin III	1.6 1.1	242 170

\* Too small an amount to weigh.

from the urine. In case 3 the patient had obstructive jaundice with considerable biliary cirrhosis and coproporphyrin I only was obtained. Coproporphyrins I and III were isolated from the urine of a patient who had syphilitic hepatitis complicated by a certain amount of biliary cirrhosis (case 4). Coproporphyrin I only was obtained from the urine of a patient who had extensive hepatic metastasis from carcinoma of the rectum (case 5). From the urine of a patient who had subacute atrophy of the liver coproporphyrins I and III were isolated (case 6), and copro-

patients were on a completely meat-free diet throughout the period of observation. The urinary coproporphyrin was isolated and esterified by the method described by Giotepass,<sup>5</sup> and the melting point of the methyl ester was determined with the Johns micro melting point apparatus manufactured by the Fisher Scientific Company. This method of isolation of coproporphyrin could not be considered at

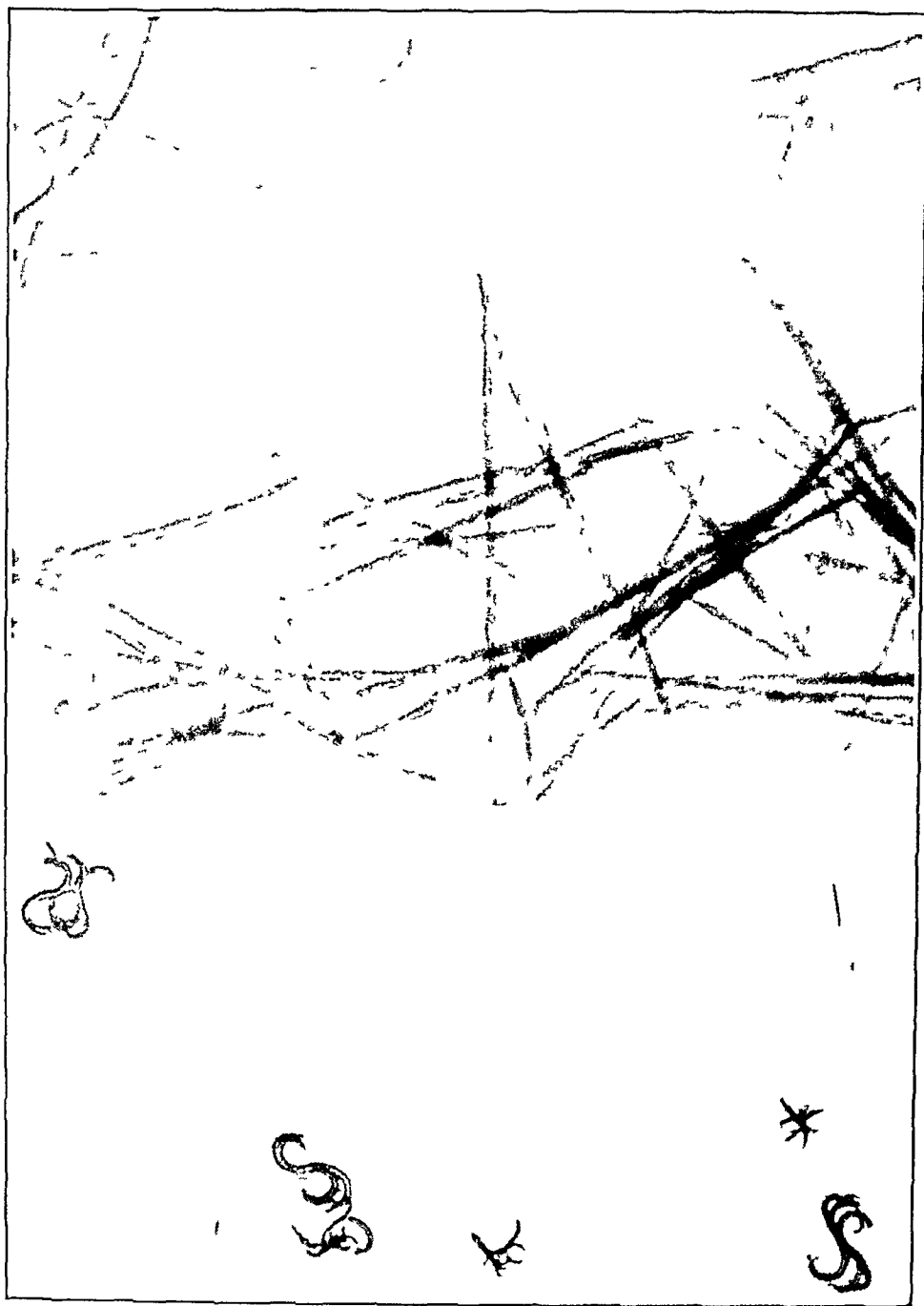


Fig 2—Crystals of coproporphyrin III methyl ester ( $\times 800$ )

all a quantitative procedure, but was used only as a means of determining the isomeric type. It was obvious that considerable loss occurred during the time of collection and adsorption, as well as during the process of purification and isolation. Figure 1 represents several photomicrographs of crystals of coproporphyrin I which were isolated during this study, and figure 2 represents photo-

# COPPER AND IRON IN HUMAN BLOOD

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Copper and iron are essential elements in the human organism, and recent enlightening research has given increased evidence of their importance in the blood stream

In our first experiments, nine years ago, on the iron content of whole blood, we found it necessary to establish a large series of determinations on normal persons<sup>1</sup> The average iron content of whole blood for 200 men was  $50.13 \pm 0.15$  mg per hundred cubic centimeters, and for 100 women it was  $43.42 \pm 0.19$  The mathematical index, the mode, the figure which appears most frequently in the series of determinations and around which the majority of figures group themselves, was 50 mg of iron per hundred cubic centimeters for 200 men and 45 mg for 100 women<sup>1b</sup> The fact that in women the average fell below the mode illustrates the tendency toward the anemic state in women

The determination of iron in whole blood is an accurate method of hemoglobin determination, and it compares favorably with the accepted method of determining oxygen capacity<sup>2</sup> Iron represents 0.335 per cent by weight of the hemoglobin molecule This is called the Butterfield factor<sup>3</sup>

hemoglobin =  $\frac{\text{mg of iron in 100 cc of blood}}{3.35} = \text{Gm of hemoglobin in 100 cc of blood}$

In our series the normal hemoglobin value based on determinations of iron in the blood of 200 men was  $14.96 \pm 0.045$  Gm per hundred cubic centimeters of blood For 100 women the normal value was  $12.96 \pm 0.06$  Gm We agree with other investigators that in the estimation of hemoglobin it is impossible to assume a normal standard for men, women and children

Children<sup>4</sup> follow a different standard than adults, especially during the first year of life They follow a curve rather than a single standard, if the figures are to be expressed on a percentage basis We found that the curve for the iron content of whole blood followed the pattern of the curves that others reported for

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1 (a) Sachs, A., Levine, V. E., and Appelsis, A. Iron in Human Blood, *Arch Int Med* **52** 366 (Sept) 1933 (b) Sachs, A., Levine, V. E., and Fabian, A. A. Copper and Iron in Human Blood, *ibid* **55** 227 (Feb) 1935

2 Karshan, M., and Freeman, R. G., Jr. Study of Hemoglobin Methods, *J Lab & Clin Med* **15** 74 (Oct) 1929

3 Butterfield, E. Ueber die Lichtextinktion, das Gasbindungsvermogen und den Eisengehalt des menschlichen Blutfarbstoffs in normalen und krankhaften Zustanden, *Ztschr f physiol Chem* **62** 173, 1909

4 Sachs, A., Levine, V. E., and Fabian, A. A. Copper and Iron in Human Blood Normal Children, *Arch Int Med* **58** 523 (Sept) 1936



porphyrin I alone was isolated from the urine of a patient who had atrophic cirrhosis of the liver of unknown cause (case 7). The urine from 3 patients who had alcoholic cirrhosis of the liver was examined, in 2 instances both coproporphyrin I and coproporphyrin III were isolated, but in 1 instance coproporphyrin III alone was demonstrated.

#### SUMMARY AND CONCLUSIONS

Ten patients who had various types of hepatic damage or biliary obstruction and who were maintained on a meat-free diet were studied. The urinary coproporphyrin of these patients was isolated and the isomeric type determined. From the urine of 6 of these patients, more than half of those on whom such studies were undertaken, both coproporphyrin I and coproporphyrin III were isolated. In 3 instances (cases 1, 4 and 9) coproporphyrin III represented but a relatively small fraction of the total coproporphyrin which was isolated, whereas in 3 other instances (cases 2, 6 and 10) a greater proportion of the coproporphyrin isolated was coproporphyrin III. In 3 cases (3, 5 and 7) coproporphyrin I alone was isolated, and in but a single case (8) was coproporphyrin III alone isolated. In each instance an appreciable quantity of coproporphyrin remained in the mother liquor, which was deeply colored. In all probability this was the methyl ester of coproporphyrin III, which crystallizes with considerably more difficulty than does the methyl ester of coproporphyrin I. It is possible that by the use of a more quantitative procedure, such as was described recently by Watson<sup>10</sup> both coproporphyrin I and coproporphyrin III might be demonstrated in the urine of all or most patients who have hepatic disease. The occurrence in the urine of these patients of coproporphyrin I, either alone or with additional varying proportions of coproporphyrin III, is in accord with the current hypotheses of synthesis and excretion of porphyrin. It is difficult on this basis to explain the excretion of coproporphyrin III alone, which occurred in but 1 instance.

The Mayo Clinic

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<sup>10</sup> Watson, C. J., and Schwartz, S. A Method of Separating Small Quantities of the Coproporphyrin Isomers 1 and 3, *Proc Soc Exper Biol & Med* **44** 7-10 (May) 1940.

averaged 40.61 mg of iron per hundred cubic centimeters of whole blood. The ages were from 1½ months to 15 years.

Fifty milligrams of iron for normal males, 45 mg for females and 40 mg for children of both sexes up to 15 years of age represent the mode for the iron content of whole blood. By means of the Butterfield<sup>3</sup> factor it was determined that 71 children had 12.10 Gm of hemoglobin per hundred cubic centimeters of blood. A normal child would thus register 80 per cent hemoglobin on the ordinary clinical hemoglobinometer, which employs one standard for comparison of all bloods regardless of age or sex of the subject. We have used the following formulas:

Milligrams of iron in 100 cc of blood  $\times 2$  = per cent hemoglobin for men

Milligrams of iron in 100 cc of blood  $\times 2.22$  = per cent hemoglobin for women

Milligrams of iron in 100 cc of blood  $\times 2.50$  = per cent hemoglobin for children

Figure 2 shows the curves made from determinations of copper and iron in the blood from birth to adult life and also shows that the content of each in the blood of both males and females remains the same up to the age of puberty. It

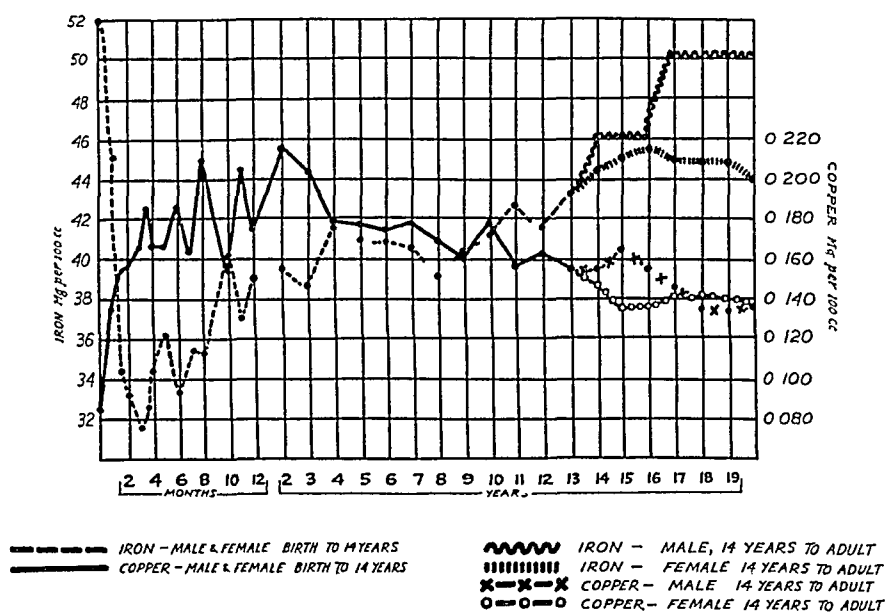


Fig. 2—Values of copper and iron in the blood of males and females from birth to the adult state

likewise shows that the iron content reaches the adult level earlier in females than in males. In girls after the fourteenth or fifteenth year of life the values for iron and hemoglobin become rather constant and assume the adult state, while, on the other hand, in boys they increase only slightly between the ages of 14 and 16 but rise sharply after the sixteenth year to reach the real adult state by the seventeenth year. The copper values follow the same scheme in reaching the adult level. This is in accord with other evidences of earlier maturity in girls. The level of iron in the blood of children is 20 per cent lower than that in adults but the relationship of iron and copper is maintained. The hypoferronemic picture is accompanied by a relative hypercupremic picture, and the hypocupremia of the newborn is associated with hyperferronemia.

The inverse relationship of the copper and the iron content of whole blood is true from infancy throughout adult life and likewise in practically all types of anemia that we have thus far encountered.

The reciprocal relationship of copper and iron is best shown in observations on patients with polycythemia, whose red blood cells and hemoglobin values can be

the hemoglobin content.<sup>5</sup> There is a sudden drop in both iron and hemoglobin immediately post partum and a secondary drop in the third month of life. The immediate drop of hemoglobin is supposedly due to a physiologic adaptation of the newborn infant to its extrauterine environment, and the secondary drop may be due to an iron depletion of the storehouses or it may represent the point in an infant's life at which adjustment finally is made in the digestive and absorptive processes to insure the utilization of the extrinsic supply of hemopoietic agents.

### HEMOGLOBIN CURVES

After the first year of life, the iron curve shows nothing unusual other than a gradual rise to the level for adults. It is necessary to follow this curve so that proper indications for iron therapy may be thoroughly understood. No amount of iron therapy thus far recorded has seemed to influence this sudden drop in the hemoglobin at birth. The difference in iron and hemoglobin values for sex are not observed until after adolescence.

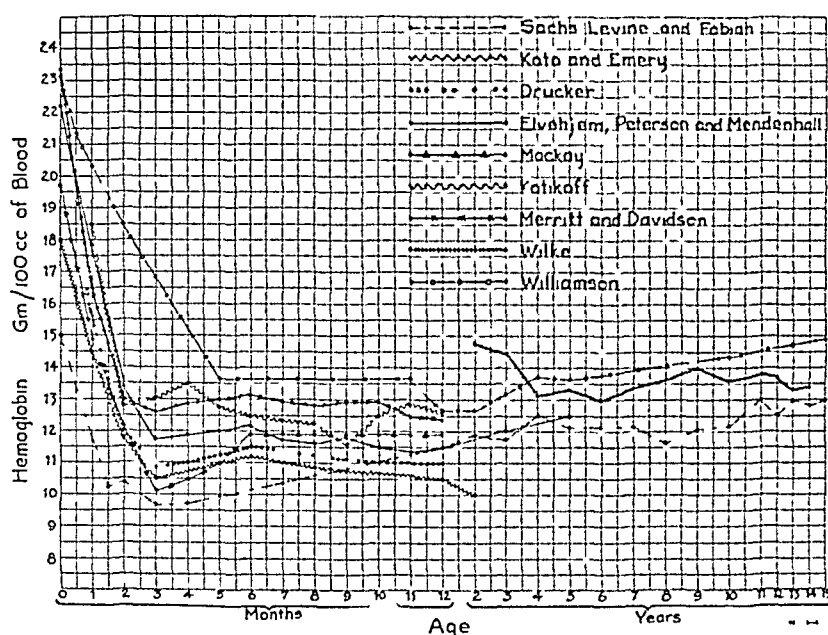


Fig 1—Hemoglobin values for blood of normal children, reported by various authors

If for clinical purposes one wishes to follow a common standard, which represents 100 per cent hemoglobin, for men, women and children, some formula or modification may be of value, because they each present a separate picture. Excluding iron values for newborn infants, the series of 71 specimens from children

<sup>5</sup> (a) Williamson, C. S. Influence of Age and Sex on Hemoglobin, *Arch Int Med* **18** 505 (Oct) 1916. (b) Wilke, E. Ueber den Gehalt des Blutes gesunder Kinder vom zweiten bis vierzehnten Lebensjahr an roten Blutkörperchen, an Blutfarbstoff, an Retikulo-cyten und an Thrombocyten, *Folia haemat* **52** 291, 1934. (c) Merritt, K. K., and Davidson L. T. The Blood During the First Year of Life, *Am J Dis Child* **46** 990 (Nov) 1933. (d) Kotikoff, I. A. Ueber den Eisengehalt im Blute der Säuglinge, *Jahrb f Kinderh* **132** 180 (July) 1931. (e) Mackay, H. M. M. The Normal Hemoglobin Level During the First Year of Life. Revised Figures, *Arch Dis Childhood* **8** 221 (June) 1933. (f) Elvehjem C. A., Peterson, W. H., and Mendenhall, D. R. Hemoglobin Content of the Blood of Infants, *Am J Dis Child* **46** 105 (July) 1933. (g) Drucker, P. Investigations on the Normal Values for the Hemoglobin and the Cell Volume in the Small Child, *Acta paediat* **3** 1, 1923. (h) Kato, K., and Emery, O. J. Hemoglobin Content of the Blood in Infancy, *Folia haemat* **49** 106, 1933.

The average copper content of 25 pregnant women was 0.195 mg per hundred cubic centimeters of blood, which is far greater than the normal, 0.131 mg per hundred cubic centimeters of whole blood, for nonpregnant women. The hypercupremia of pregnancy when associated with a normal iron content is physiologic and reflects the normal mechanism of transporting copper from the maternal blood to the fetal reservoirs. The hypercupremia of pregnancy when accompanied by a hypoferronemia may represent not only this mechanism but also mobilization of copper to combat the anemia which is commonly found in some pregnant women.

The fetus, on the other hand, has a low copper content of the blood and a relatively high iron content. This high iron content is maintained even when the maternal blood shows definite hypoferronemia. The average iron content of fetal blood was 54.34 mg per hundred cubic centimeters, while the average copper content was 0.098 mg. These figures may vary slightly but represent a fairly normal average. After diffusion of the copper through the placenta, the fetus does not retain most of this element in the blood stream but evidently stores it in the liver.

The polycythemia of newborn infants was not evident in our series. The blood counts reported by several authors varied because some used cord blood and others used capillary blood for the counts. Erythrocyte counts on capillary blood are universally higher than counts on cord blood. Our averages show that capillary counts exceed cord counts by 1,000,000 cells per cubic millimeter in normally born infants and by 700,000 in infants born by cesarean section.<sup>9</sup>

The reciprocal relationship of copper and iron is present in all forms of anemia that we have been privileged to examine. We have thus far never encountered a deficiency of copper, and it is rather difficult to conceive how a true deficiency could exist, unless a very abnormal nutritional state were present. The small amount of copper required daily and its occurrence in all foods, in water, in beverages, in iron compounds and even in dust make the intake ample. Starvation, high intestinal fistulas and extremely severe diarrhea are possible factors encouraging a deficiency of copper, but as yet no one has definitely shown a deficiency of this element in the blood stream of a human being.

The inverse relationship of copper and iron usually is constant, but occasionally copper fails to respond to a fall in iron. One such occurrence is nephritis. One of our patients with chronic nephritis had 30.95 mg of iron per hundred cubic centimeters of whole blood and a blood copper content of 0.180 mg. This was a normal response. However, as the disease progressed and the anemia became more severe, the iron content fell to 22.05 mg but the copper content failed to rise, it dropped to 0.145 mg. In another female patient with chronic nephritis, the iron content of the blood was 33.9 mg per hundred cubic centimeters and the copper content 0.123 mg. These figures represent a hypoferronemia without a hypercupremia. If much albumin is present, more copper is excreted in the urine.

In a splenectomized patient the copper content occasionally fails to respond to a drop in iron, but this seems temporary and as the patient adjusts himself to his splenectomy normal values soon occur. The function of the spleen in copper metabolism is not well understood. It is one of the chief storehouses for copper, but other than this no definite function in copper metabolism can yet be assigned to the spleen.

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9 Sachs, A., Levine, V. E., Griffith, W. O., and Hansen, C. H. Copper and Iron in Human Blood. Comparison of Maternal and Fetal Blood After Normal Delivery and After Cesarean Section, *Am J Dis Child* 56:787 (Oct.) 1938.

readily reduced by phenylhydrazine. Hypoferronemia was followed by hypercupremia, and hyperferronemia was followed by hypocupremia. This is best shown in figure 3.

In experimental hemorrhage in dogs and in the massive hemorrhage of peptic ulcer the reciprocal relationship of copper and iron is again emphasized.<sup>6</sup> Elvehjem<sup>7</sup> and the Wisconsin group have called attention to the action of copper and iron in synthesis of hemoglobin, and we feel that the reciprocal relationship of copper and iron also emphasizes the importance of copper. It acts as a catalyzer and likewise must aid in the mobilization of iron when needed from its storehouse. The fetal liver is the most important storage organ for both copper and iron. The fetal liver contains six to ten times as much copper per kilogram of weight as the adult liver. Sheldon<sup>8</sup> stated that 7 mg of copper is stored in the liver of the newborn infant.

A normal mother constantly supplies the fetal liver with both iron and copper. The blood volume increases during pregnancy and at term rises to the extent

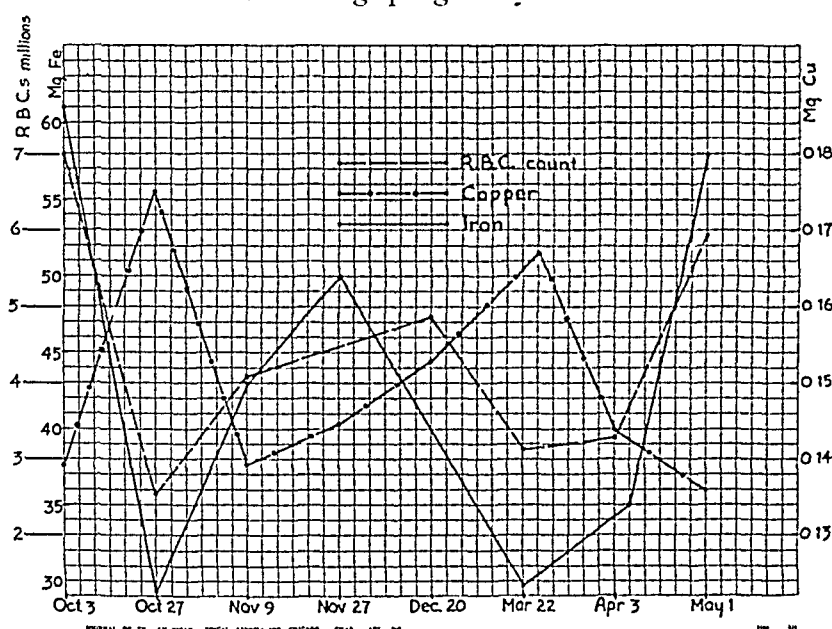


Fig 3—Fluctuation of iron and copper values in the blood of a patient with polycythemia vera

of 23 per cent. The total amount of copper in the blood stream during pregnancy may be almost twice the amount in the nonpregnant state.

The iron content of whole blood during pregnancy was of two significant types: one was normal or slightly below normal, and the second showed a true anemia. Both types were accompanied by a high copper level. The average iron content of 25 pregnant women<sup>1b</sup> was 40.44 mg per hundred cubic centimeters of blood, which is a figure below the normal, 45 mg, for nonpregnant women. This relative anemia, or physiologic anemia, as it is called by some, varies in different women and may be combated by iron therapy.

6 Sachs, A. The Effect of Bleeding Ulcers and Hemorrhagic Anemia upon Whole Blood Copper and Iron, *Am J Digest Dis & Nutrition* 4:803 (Feb) 1937.

7 Elvehjem, C. A., and Sherman, W. C. Action of Copper in Iron Metabolism, *J Biol Chem* 98:309 (Oct) 1932. Elvehjem, C. A., Steenbock, H., and Hart, E. B. Is Copper a Constituent of the Hemoglobin Molecule? *ibid* 83:21 (July) 1929.

8 Sheldon, J. H. Some Consideration on the Influence of Copper and Manganese on the Therapeutic Activity of Iron, *Brit M J* 2:869 (Nov 12) 1932.

been shown to be closely related to respiratory enzymes and to various undetermined substances in animal cells. This relationship demands attention because of its bearing on transportation and interchange of iron in the organism.

*Ferrification*—This term is used to denote deposition of iron in inflammatory areas. The mobilization and deposition in areas of inflammation have been described fully by Menkin,<sup>16</sup> and she has advanced a definite protective function for iron in tuberculous lesions. Iron accelerates growth of connective tissue cells, a fact which suggests that it may aid in tissue repair. Excessive deposits of iron in various types of hepatic cirrhosis are also accompanied by fibrosis.<sup>17</sup>

*Hemoglobin Production*—Iron is one of the most essential parts of the hemoglobin molecule and is the most important factor in iron deficiency anemias.

*Iron Transportation*—The serum iron is the transport iron and has been previously mentioned. The exchange of iron between the circulating blood and the tissue cells is still an unsolved problem. It is known that very little of the absorbed iron is excreted and most of it is conserved and reutilized.

#### FUNCTIONS OF COPPER

The functions of copper are not as clearly understood as those of iron. Copper acts as a catalyst with reference to growth, respiration and hemopoiesis.

*Growth*—The earliest function assigned to copper was that of a promoter of growth. This was found in its relationship to plants. Copper increased the growth of plants unless present in too concentrated amounts, in which case it inhibited growth.<sup>18</sup> Rats maintained on a diet rich in copper showed a greater increase in weight than those on a diet restricted as to copper.<sup>19</sup>

The liver of the embryo and that of the newborn animal of most species contain higher percentages of copper than the liver of the adult of the same species.<sup>20</sup> In man<sup>21</sup> the same is true, and this high percentage of copper in the fetal liver is necessary so that its storehouses will not be depleted during the first few months of infancy, when the diet may be low in copper. This fact was demonstrated in the figures previously shown during pregnancy.<sup>22</sup> The mother is constantly trying to fill the liver of the fetus with copper in order to prepare it for its early life.

*Respiration*—Copper plays an important role in the respiratory process of certain crustaceans and mollusks. Hemocyanin is the respiratory pigment of these animals. Copper bears the same relationship to hemocyanin as iron does to hemoglobin and is present in about the same proportion.<sup>23</sup> Copper accelerates

16 Menkin, V. Studies on Inflammation, Fixation of Metal in Inflamed Areas, *J. Exper. Med.* **51** 879 (June) 1930, Accumulation of Iron in Tuberculous Areas, *Am. J. M. Sc.* **185**:40 (Jan.) 1933.

17 Sachs, A., and Russum, C. Hemochromatosis, *Nebraska M. J.* **22** 121 (April) 1937.

18 Allison, R. N., Bryan, O. C., and Hunter, J. H. Bulletin 190, Florida Agricultural Experiment Station, 1927.

19 Flinn, F. B., and Inouye, J. M. Some Physiological Aspects of Copper in the Organism, *J. Biol. Chem.* **84** 10 (Oct.) 1929.

20 Cunningham, I. J. Some Biochemical and Physiological Aspects of Copper in Animal Nutrition, *Biochem. J.* **25** 1267, 1930.

21 Morrison, D. B., and Nash, T. P., Jr. Copper Content of Infant Livers, *J. Biol. Chem.* **88** 479 (Sept.) 1930.

22 Sachs, Levine and Fabian<sup>1b</sup> Sachs, Levine, Griffith and Hansen<sup>9</sup>

23 McCollum, E. V., Orent-Keiles, E., and Day, H. G. The Newer Knowledge of Nutrition, ed. 5, New York, The Macmillan Company, 1939, p. 211.

## FUNCTION OF IRON

There are four forms of iron, namely, hemoglobin iron, plasma iron, easily split off iron and nuclear iron. The hemoglobin contains the largest share of iron and its function is well known. The plasma iron or serum iron is the transport iron, which Moore and his co-workers have so ably described<sup>10</sup>. They have shown that the values for plasma iron and serum iron are practically the same and hence have called the serum iron the transport iron. The easily split off iron was well described by Barkan<sup>11</sup> and was so termed because weak acids free it from its chemical combinations in erythrocytes and in plasma. Its function is not definitely known. The nuclear iron is comparable to the iron found in practically all cells and is part of the respiratory enzyme mechanism<sup>12</sup>.

The functions of iron in man are manifold, but there are five interesting phases in which blood iron participates, namely storage of iron, catalysis, ferrification, production of hemoglobin and transportation of iron.

*Storage*—Iron is stored chiefly in the liver, spleen, bone marrow and kidneys but is found in all cells of the body. The amount of iron in the human body varies with the age, sex, size and nutritional state of a person. A large share of the body's iron is found in the circulating blood. A normal adult has about 85 cc of blood per kilogram of body weight<sup>1</sup>. A male adult who normally has 50 mg of iron per hundred cubic centimeters of blood would have 3 Gm of circulating iron while a female adult of similar weight with normally 45 mg per hundred cubic centimeters of blood would have only 2.7 Gm of circulating iron. Chang and Harrop<sup>14</sup> found the circulating blood volume between 63 and 76 cc per kilogram of body weight. This figure was arrived at by the carbon monoxide method which yields lower values than the dye method.

The approximate total iron content of an average adult according to Fowler<sup>15</sup> is 4.5 Gm. The largest part, about 2.5 Gm, is in the circulating hemoglobin. The second largest amount, about 1.3 Gm, is in the available store bases. The third portion is found in the nuclei and cytoplasm of all types of cells in the body which is not available for use in hemoglobin regeneration. When the red cells which have completed their life cycle are destroyed in the spleen or elsewhere, the hemoglobin released is broken down into globin, bile pigment and iron. This iron is the major source of the body's iron supply.

*Catalysis*—Warburg's establishment of the respiratory ferment as an iron complex<sup>12</sup> has been a stimulus to the study of metallic catalysts and enzymes. The chromatin in the nucleus of every cell contains iron. The nuclear material dominates the metabolism of the cell. The ferruginous portion of hemoglobin, the heme, has

10 Moore, C. V., Quiligan, J. J., Jr., and Read, J. T. The Chemical Methods and Normal Values for Plasma Iron and "Easily Split-Off" Blood Iron, *J. Clin. Investigation* **15** 613 (July) 1937. Moore, C. V., Doan, C. A., and Arrowsmith, W. R. The Mechanism of Iron Transportation. Its Significance in Iron Utilization in Anemic States of Varied Etiology, *ibid* **15** 627 (July) 1937.

11 Barkan, G. Ueber das leicht abspaltbare Bluteisen und sein Verhältnis zum Hämoglobin, *Ztschr. f. physiol. Chem.* **148** 124, 1925.

12 Warburg, O. Enzyme Problem and Biological Oxidations, *Bull. Johns Hopkins Hosp.* **46** 431 (June) 1930.

13 Keith, N. M., Rowntree, L. F., and Geraghty, J. T. A Method for the Determination of Plasma and Blood Volume, *Arch. Int. Med.* **16** 547 (Oct.) 1915.

14 Chang, N. C., and Harrop, G. A., Jr. Determination of Circulating Blood Volume with Carbon Monoxide, *J. Clin. Investigation* **5** 393 (April) 1928.

15 Fowler, W. M. Iron Deficiency Anemias, *J. Omaha Mid-West Clin. Soc.* **2** 16 (Jan.) 1941.

determinations were made with the photoelectric colorimeter. Our previous analyses of copper and iron in whole blood were made by colorimetric methods, previously described.

TABLE 1—*Comparison of Average Values\* of Copper and Iron in the Blood of Normal Males and Females*

Sex	Whole Blood Copper	Whole Blood Iron	Serum Copper	Serum Iron
Males	0.132	50.0	0.084	0.154
Females	0.131	45.0	0.098	0.139

\* Expressed in milligrams per hundred cubic centimeters

TABLE 2—*Determinations\* of Iron and Copper in the Blood of Normal Male Adults*

Name	Age	Red Blood Cell Count	Hemo- globin, Gm per 100 Cc	Serum Iron	Serum Copper	Whole Blood Copper	Whole Blood Iron
1 Hils	20	4,800,000	13.1	0.168	0.076	0.105	44.0
2 Hasi	21	5,216,000	14.8	0.127	0.087	0.098	49.6
3 Arch	22	5,760,000	16.8	0.162	0.086	0.090	56.4
4 Fitz	22	5,984,000	14.8	0.181	0.071	0.100	49.6
5 Dem	23	5,504,000	16.3	0.192	0.080	0.094	54.8
6 Addi	23	4,896,000	13.4	0.147	0.089	0.109	45.2
7 Gabr	24	4,864,000	14.9	0.176	0.104	0.101	50.0
8 Ande	25	5,408,000	15.2	0.118	0.080	0.100	51.2
9 Egan	25	5,408,000	15.2	0.107	0.070	0.103	51.2
10 Dew	27	5,472,000	16.8	0.159	0.084	0.106	56.4
Average	23	5,331,000	15.1	0.154	0.084	0.102	50.8
Range	20 to 27	4,800,000 to 5,984,000	13.1 to 16.8	0.107 to 0.192	0.070 to 0.104	0.090 to 0.109	44.0 to 56.4

\* Expressed in milligrams per hundred cubic centimeters

TABLE 3—*Determinations\* of Iron and Copper in the Blood of Normal Female Adults*

Name	Age	Red Blood Cell Count	Hemo- globin, Gm per 100 Cc	Serum Iron	Serum Copper	Whole Blood Copper	Whole Blood Iron
1 Dobe	20	4,448,000	13.9	0.069	0.089	0.104	46.8
2 Lark	21	4,992,000	14.0	0.190	0.124	0.121	47.2
3 Marc	22	4,576,000	13.4	0.100	0.088	0.105	45.2
4 Vaug	23	4,864,000	12.7	0.108	0.104	0.108	42.8
5 Arkr	23	4,672,000	13.3	0.181	0.100	0.107	44.8
6 Hick	25	4,672,000	13.9	0.168	0.108	0.102	46.8
7 Tull	24	4,200,000	14.3	0.182	0.092	0.105	48.0
8 Hugh	25	4,480,000	13.4	0.122	0.078	0.101	44.0
9 Shep	25	4,384,000	13.4	0.125	0.098	0.114	44.0
10 Jenn	28	4,544,000	12.4	0.149	0.100	0.106	41.6
Average	23	4,583,000	13.5	0.130	0.098	0.107	45.1
Range	20 to 28	4,200,000 to 4,992,000	12.4 to 14.3	0.069 to 0.190	0.078 to 0.124	0.101 to 0.121	41.6 to 48.0

\* Expressed in milligrams per hundred cubic centimeters

The iron content of serum as well as of whole blood is lower in females than in males. The copper content of serum and of whole blood is relatively high in females. This is in accord with the relative anemic tendency reflected in all female bloods.



oxidation of iron.<sup>24</sup> The oxidation of glutathione is accomplished by the action of copper, whereas iron and other metals fail in this capacity.<sup>25</sup>

*Hemopoiesis*—Copper seems essential to hemopoiesis, although it is not part of the hemoglobin molecule. Stein and Lewis<sup>26</sup> have definitely shown it to be an important factor in erythropoiesis. Elvehjem and his co-workers have shown what an important part it plays in hemoglobin formation, namely, that of a catalyst. We have demonstrated that copper is an essential element in hemopoiesis because in any type of anemia copper is called forth to mobilize iron from the storehouses as evidenced by its rise in the whole blood when iron falls. This is especially well shown in bleeding experiments on dogs and likewise in massive hemorrhage from bleeding peptic ulcers.

Copper is transported in the plasma or serum the same way as iron. We have demonstrated in our experiments on dogs that oral administration of copper sulfate is followed by a substantial increase in the copper in the blood serum, as is shown by figure 4.

The dogs were made to fast for eighteen hours, after which we established a basal copper level in the serum from hour to hour for seven hours. The fasting

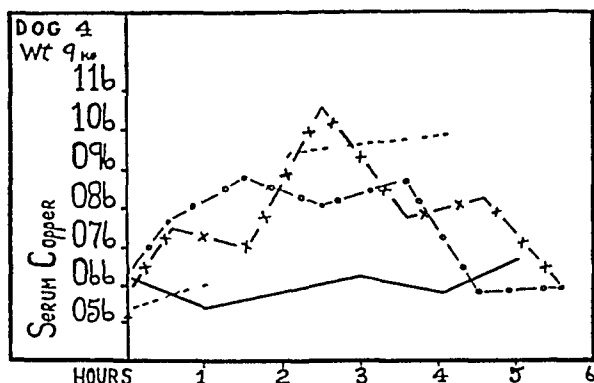


Fig 4—Rise in serum copper (expressed in milligrams per hundred cubic centimeters) following oral administration of copper sulfate. Solid line indicates basal level, broken line with x's, values after a dose of 2 mg of copper sulfate per kilogram, broken line with circles values after a dose of 8 mg of copper sulfate per kilogram, broken line, values after a dose of 16 mg of copper sulfate per kilogram.

values for serum copper remained practically constant. Different doses of copper sulfate were used, 2, 8 and 16 mg per kilogram of body weight. The dogs retained the 2 and the 8 mg doses but vomited after the 16 mg dose. All showed a definite rise in the copper content of the blood serum.

Our experiments with administration of copper to human beings are not completed at this time but will be reported later. Our averages of copper and iron in whole blood and in serum of normal males and females are shown in table 1.

Our recent analyses of the copper and iron content of whole blood and serum of 10 normal men and 10 normal women are shown in tables 2 and 3. These

24 Quartaroli, A. Il binomino ferro-rame in chimica e in biologia, Ann di chim applic 22 517, 1932.

25 Voegtlin, C., Johnson, J. M., and Rosenthal, S. M. Catalytic Action of Copper in Oxidation of Crystalline Glutathione, Pub Health Rep 46 2234 (Sept 18) 1931.

26 Stein, H. B., and Lewis, E. C. Stimulating Action of Copper on Erythropoiesis, J Nutrition 6 465 (Sept) 1933.

The treatment of iron deficiency anemia is on a more rational basis than in previous years. Iron must be in an ionizable form before it can be absorbed. This is true whether it is in an organic or an inorganic form. The amount of iron required each day varies with age, sex and size of the person. It has been estimated that 5 to 15 mg of iron constitutes the daily requirement. Different authors have reported various amounts, but these seem to be the most frequently

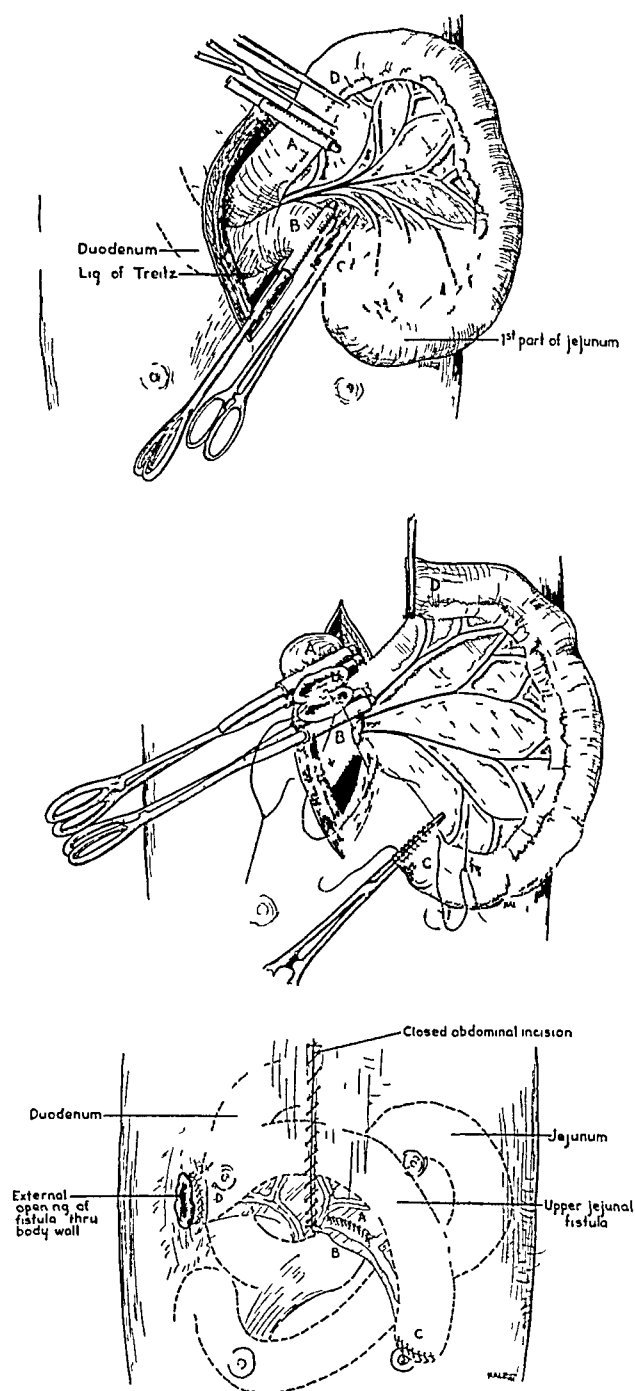


Fig 6—Drawings illustrating technic of making Thiry fistula loops in dogs

quoted figures. They are based on very carefully performed balance studies by Fowler<sup>15</sup> and his associates. Iron is excreted largely in the bile, feces and urine.

The figures reported for the daily requirements of copper have not been as widely accepted as the figures for iron. Some authors set the daily amount at 2 mg. Chou and Adolph<sup>28</sup> maintained that the copper intake should be 2 mg

28 Chou, T. P., and Adolph, W. H. Copper Metabolism in Man, *Biochem J* **19** 476, 1935

## ABSORPTION OF IRON AND COPPER

Moore and his co-workers<sup>27</sup> have shown that iron is absorbed chiefly in the duodenum, to some extent in the jejunum and to a lesser extent in the ileum. They did their work in human beings by use of the Miller-Abbott tube. We have performed experiments on absorption of iron in isolated loops in dogs and have corroborated their findings on absorption. Iron was absorbed in the upper and middle jejunal loops but very slightly in the distal loop. We also investigated absorption of copper. Copper was absorbed in the upper jejunal loop, but practically not at all in the middle and distal loops.

The Thiry fistula loops were made in all dogs, and the technic used was as follows:

With intratracheal ether anesthesia and with the usual sterile precautions, the abdomen was opened through a midline incision about 4 inches (10 cm) long. The first loop of the jejunum was identified, and about 2 feet (60 cm) of the bowel was marked off with an Allis forceps. This segment of bowel was separated from the remainder of the jejunum, by means of rubber-covered clamps on the part to be anastomosed and a Kocher forceps on the part which was to form the fistula. Continuity of the intestinal tract was restored by end to end

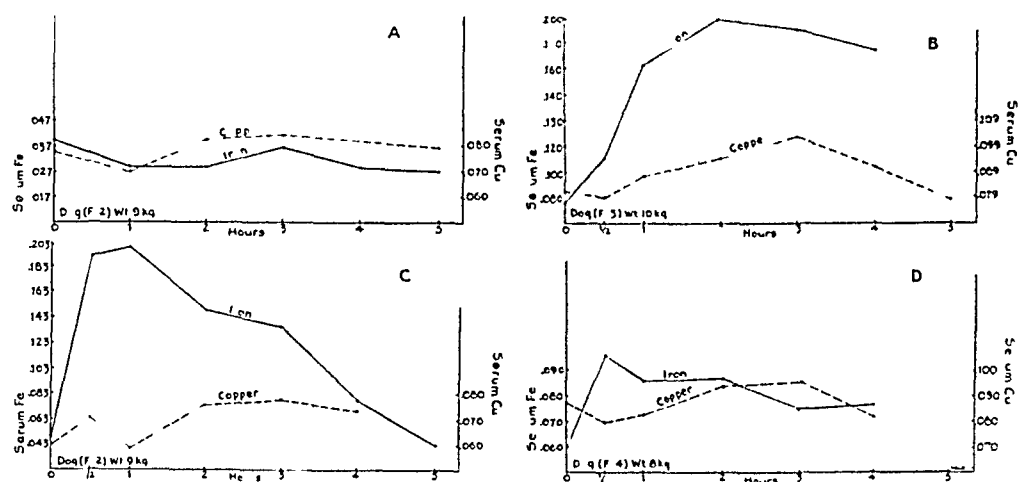


Fig 5—Studies of iron and copper in the serum (expressed as milligrams per hundred cubic centimeters). *A* Relative constancy during a five hour period. *B* Definite absorption of iron and some absorption of copper from a loop of proximal jejunum, after 3 mg of ferrous sulfate and 1 mg of cupric sulfate per kilogram. *C* Definite absorption of iron and slight or no absorption of copper from a loop of midjejunum, after a dose of 3 mg of ferrous sulfate and 1 mg of cupric sulfate per kilogram. *D* Slight or no absorption of iron and copper from a loop of distal jejunum, after a dose of 3 mg of ferrous sulfate and 1 mg of cupric sulfate per kilogram.

suture with two layers of silk. The distal end of the separated loop was closed and inverted over a Kocher clamp, and the other end of the bowel was brought out through a stab wound in the right rectus muscle and was anchored in place by sutures through the peritoneal and outer coat of the bowel. The abdominal incision was closed in layers by the usual method.

Fistulas of this type were made in the upper, the middle and the lower loop of the jejunum in different animals, as illustrated in figure 6.

<sup>27</sup> Moore, C V, Bierman, H O, Minnich, V, and Arrowsmith, W R. Studies in Iron Absorption with Special Reference to the Relationship of Iron Metabolism to Ascorbic Acid, in Blood, Heart and Circulation. Symposium, Publication 13, American Association for the Advancement of Science, Washington, D C, 1940, pp 34-37. Moore, C V, Arrowsmith, W R, Welch, J, and Minnich, V. Studies in Iron Transportation and Metabolism. Observations on the Absorption of Iron from the Gastro-Intestinal Tract, *J Clin Investigation* 18:543 (Sept) 1939.

When iron is prescribed it must be noted whether the patient actually takes it, otherwise the therapeutic results will prove perplexing. Many patients claim that they are taking the medication but in reality are not. Persons may react differently and better to one form of iron than to another. Ferrous salts are most easily absorbed.

It is claimed that lack of vitamin B<sub>12</sub> can produce anemia,<sup>1</sup> but at present the application of this vitamin to the treatment of anemia is in the experimental stage. Expensive products containing liver extract, vitamins, copper and iron are of no more value than simple ferrous sulfate. If a vitamin deficiency does exist, the amount of vitamin administered in expensive preparations may not be adequate to cover the deficiency. Occasionally liver extract in adequate doses given with iron seems to have value and should be used. The use of cobalt has been recommended, but as yet its employment therapeutically has been too limited to permit an opinion relative to its efficiency.

When iron is given, it must be ascertained that it is being absorbed and is producing an adequate hemopoietic response. If this response is insufficient, the reasons must be sought. The two most important reasons for failure of iron therapy in anemia are continued hemorrhage and infection. Some anemias, however, do not respond to treatment, and no satisfactory explanation can be found for such failures.

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a day for adults Sherman<sup>29</sup> likewise gave 2 mg of copper as the daily needs. Other authors stated that a 70 Kg man requires 7 mg of copper per day<sup>30</sup>. Some give the daily needs of children to be 0.6 mg of available iron and 0.1 mg of copper per kilogram of body weight<sup>29</sup>.

Copper is mostly excreted in the feces and urine. The most iron and copper that is lost is usually lost by hemorrhage. The adult body is said to contain from 100 to 150 mg of copper<sup>29</sup>. With an intake of 2.17 mg, the excretion through the bowel was 1.22 mg and in the urine 0.27 mg<sup>29</sup>.

A great controversy exists as to whether copper is or is not needed in addition to iron to combat certain types of anemia. Most clinicians have found it unnecessary to add copper. We have never found a copper deficiency in analyses of the blood that we have made and do not feel that added copper is needed in the treatment of iron deficiency anemias.

Copper is present in abundance in liver, oysters, nuts and legumes and is present in varying quantities in all types of food. Water, milk and all other liquids contain copper. All iron pharmaceutical products contain copper. Dust contains variable amounts of copper. In fact, it is hard to get copper-free materials to prevent contamination with copper in analyses for that element. It is true that a milk diet is a copper-poor diet, but most diets have more than an ample supply of copper. We feel that one of the best guides to an adequate intake of iron is the rise in the reticulocyte count. Moore stated that when using this as a guide he has never found a secondary reticulocyte response or any evidence of more rapid regeneration of hemoglobin after copper was added than was obtained by iron alone<sup>31</sup>.

The nutritional anemias of infants are a problem that needs further study before one can definitely say whether or not copper is needed. In the cases we have been privileged to examine we have found no copper deficiency to date.

The ferrous salts are more readily absorbed than the ferric salts. Hydrochloric acid seems of great value in ionizing iron and hence in making it more available. Iron must be available whether it is organic or inorganic. Foods vary from 20 per cent for some leafy vegetables to 100 per cent for egg yolks in availability of iron supply.

The calcium-phosphorus ratio may have some bearing on absorption of iron. Phosphorus interferes with the absorption of iron experimentally, and calcium can prevent this interference and thus assures efficient utilization of iron. Clinically this as yet seems to be of little importance with adequate diets. Absence of free hydrochloric acid cannot be supplied by the addition of dilute hydrochloric acid, but nature accommodates itself to its needs, as is readily seen in patients with idiopathic hypochromic anemia who have no free acid.

Infections, diarrheas or deficiency diseases may interfere with absorption of iron. Hemorrhage is the chief cause for loss of iron. Growth demands more iron both for increase in the supply needed and for increase in the blood volume. Pregnancy needs careful observation because greater demands are present and the fetus must be adequately supplied. Twin pregnancies and premature infants demand close attention because the supplies may not be adequate.

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29 Harrow, B. Text Book of Biochemistry, Philadelphia, W. B. Saunders Company, 1940.

30 Conferences on Therapy [from Cornell University Medical School and New York Hospital] Treatment of Blood Disorders, The Use of Iron and Other Metals, J. A. M. A. **114** 2301 (June 8) 1940.

31 Moore, C. V., in Round Table Discussion on the Therapeutics of Anemia, J. Pediatr. **17** 554 (Oct) 1940.

becoming worse, and that he had had edema of the ankles for two months. These symptoms continued in varying degree throughout the remainder of his life. He was admitted to the hospital on eleven different occasions (nine times to the Brooklyn Hospital and twice to Kings County Hospital). In 1936 a visible heaving pulsation was noted (at the Brooklyn Hospital), and in June 1937 a definite diagnosis of aneurysm of the left ventricle was established by roentgen examination. In October 1937 the physical examination revealed that he was suffering from cardiac decompensation. The pulse rate was 84 beats per minute and the blood pressure 108 systolic and 82 diastolic. There was a marked precordial pulsation, separate from the apex beat, in the third intercostal space. There was no thrill. The heart sounds were diminished, and there was a systolic murmur at the apex. The lungs showed bilateral pleural effusion, and there was edema of both ankles. The Wassermann reaction was negative. The electrocardiogram was of the type associated with previous infarction in the anterior wall of the left ventricle. The roentgenogram showed enlargement of the left ventricle. Along the upper part of the lateral border of the heart there was a bulge about 5 cm in diameter. On fluoroscopic examination there was marked systole by expansion of the sac. This was also demonstrated by kymographic examination. The patient died on Oct 10, 1939, at the Brook-

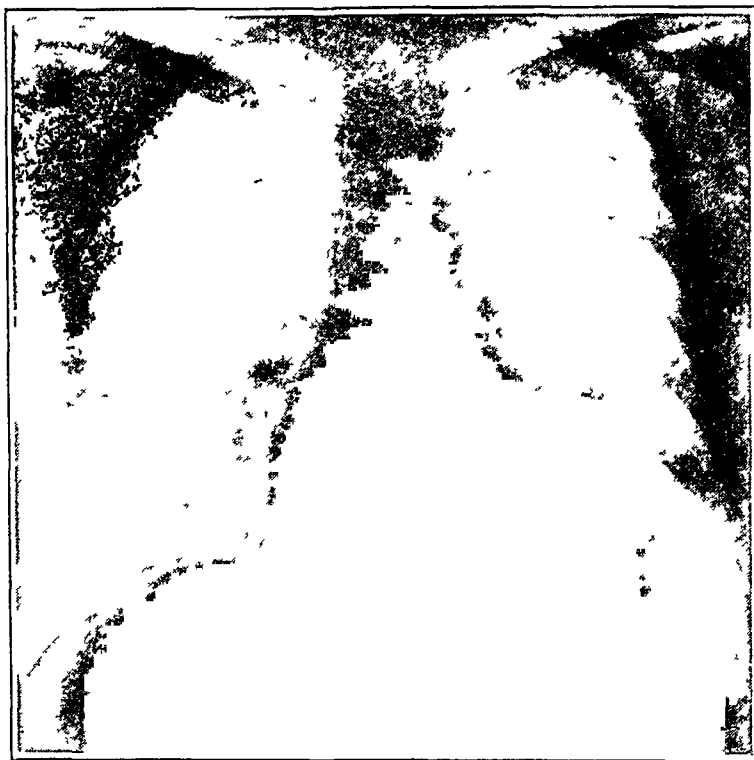


Fig 1 (case 1)—Aneurysmal bulge at the upper part of the left border

lyn Hospital, and the autopsy, performed by Dr Arnold deVeer, showed an aneurysm of the anterior surface of the left ventricle about 6 cm in diameter, the superior margin of which was 3 cm from the auriculoventricular sulcus. There was also a small aneurysmal bulging in the posterior wall of the left ventricle, to which a large thrombotic mass was adherent. The anterior descending branch of the left coronary artery was occluded slightly above the site of the aneurysm, but the circumflex branch and the main right coronary were patent. Branches of the right coronary artery supplying the posterior wall were thrombosed. Death was due to acute hemorrhagic pancreatitis from embolization to the pancreaticoduodenal artery. There was a large recent infarct in the spleen.

CASE 2—A J, a Negress aged 13,<sup>8</sup> was admitted to the cardiac clinic of Kings County Hospital in January 1938, complaining of cough and palpitation of six months' duration. The previous history showed nothing of note, and there was no history of syphilis in either the parents or child. Physical examination showed a well developed young girl who appeared in good condition. The pulse was regular in rhythm, at a rate of 96 beats per minute, and the

<sup>8</sup> This case has been reported in detail previously (Hollander, A G, and Crawford, J H. *Am Heart J* 20 762, 1940).

# ANEURYSM OF THE HEART

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Although aneurysm of the heart has been recognized for almost two centuries, it is only recently that the antemortem diagnosis has been made with any assurance. The advent of more thorough study of patients with heart disease by roentgenologic methods has considerably increased the frequency with which the correct diagnosis is made. The first account of aneurysm of the ventricle was by Galeati<sup>1</sup> in 1757, but the first detailed description of the condition was given by Matthew Baillie<sup>2</sup> in 1793. Since then, from time to time, other papers have appeared dealing with the subject. These have been fully reviewed by Hall, Steinberg,<sup>3</sup> and Parkinson, Bedford and Thomson,<sup>4</sup> who added cases of their own. The first case in which the condition was diagnosed by means of roentgen rays was reported by Sezary and Alibert<sup>5</sup> in 1922. Since then, in many of the cases reported it has been recognized by roentgen study although the diagnosis is still difficult, as is shown by the fact that in 1926 Pletnew,<sup>6</sup> in a summary of 300 cases previously described, found that in only 6 had the correct diagnosis been made antemortem. Gradually definite criteria by which the condition can be ascertained are being evolved, so it seems probable that an increasing number of cases will become recognized.

Aneurysm of the ventricular septum is usually diagnosed only post mortem, hence, in this study only aneurysms affecting the ventricular walls will be considered. It is possible that a septal aneurysm might produce the Bernheim syndrome or, if extensive that enlargement of the heart might be seen on roentgen examination. However, there are so many conditions which frequently cause enlargement of the heart that diagnosis of septal aneurysm is unlikely to be made.

The following 13 cases, in 9 of which the diagnosis was proved by autopsy, are reported because there was well marked aneurysmal dilatation of the ventricular wall. In 4 of the group in which autopsy was performed the diagnosis was made antemortem, and 3 patients are still alive. One patient presented undisputable clinical evidence of the condition, but permission for an autopsy could not be obtained.

## REPORT OF CASES

CASE 1—F. A., a white man aged 64, was admitted to the Brooklyn Hospital on June 28, 1935, suffering from severe precordial pain. A diagnosis of acute coronary occlusion was made. The infarct was situated in the anterior wall of the left ventricle. In October of this year he was readmitted to the Brooklyn Hospital, suffering from acute heart failure (left side). In February 1936 he was admitted to Kings County Hospital. He stated that he had been dyspneic, that since his illness in 1935 he had had dull precordial pain, which was gradually

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1 Galeati, D. G., cited by Parkinson, Bedford and Thomson.<sup>5</sup>

2 Baillie, M. *The Morbid Anatomy of Some of the Most Important Parts of the Human Body*, London, J. Johnson, 1793.

3 Hall, D. G. *Edinburgh M. & S. J.* **14** 322, 1903.

4 Sternberg, M. *Das chronische partielle Herzaneurysma*, Leipzig, Franz Deuticke, 1914.

5 Parkinson, J., Bedford, D. E., and Thomson, W. A. R. *Quart. J. Med.* **7** 455, 1938.

6 Sezary, A., and Alibert, T. *Bull. et mem. Soc. med. d. hop. de Paris* **46** 172, 1922.

7 Pletnew, D. D. *Ztschr. f. klin. Med.* **104** 378, 1926.

temperature remained normal. The patient's general condition gradually improved. On October 10 it was noted that a localized pulsation had developed in the region of the stab wound which was not synchronous with the apex beat. There was a marked thrill in this area, and systolic and diastolic murmurs were heard all over the precordium, the site of maximum intensity being in the area of pulsation. There was no Corrigan pulse. At this time the electrocardiogram showed a diphasic T wave in lead II and a negative T wave in lead III, while roentgen examination showed no change from the previous study. Despite this, it was felt that a diagnosis of traumatic aneurysm of the heart could be made. The patient was discharged from the hospital on November 21 with no evidence of heart failure.

CASE 4—J. M., a white man aged 65, was admitted to Kings County Hospital on Sept. 3, 1941. He had had a hemiplegia of the left side nine years before, from which he had made a satisfactory recovery. He then felt well until 1938, when he was seized one day with severe pain in the chest, lasting two to three days. This was accompanied by diarrhea and hiccup. After that time he had dyspnea on exertion, which varied in severity, but there was no recurrence of precordial pain. He had severe dyspnea when he walked and also severe nocturnal dyspnea. The legs felt as if they were paralyzed. Physical examination

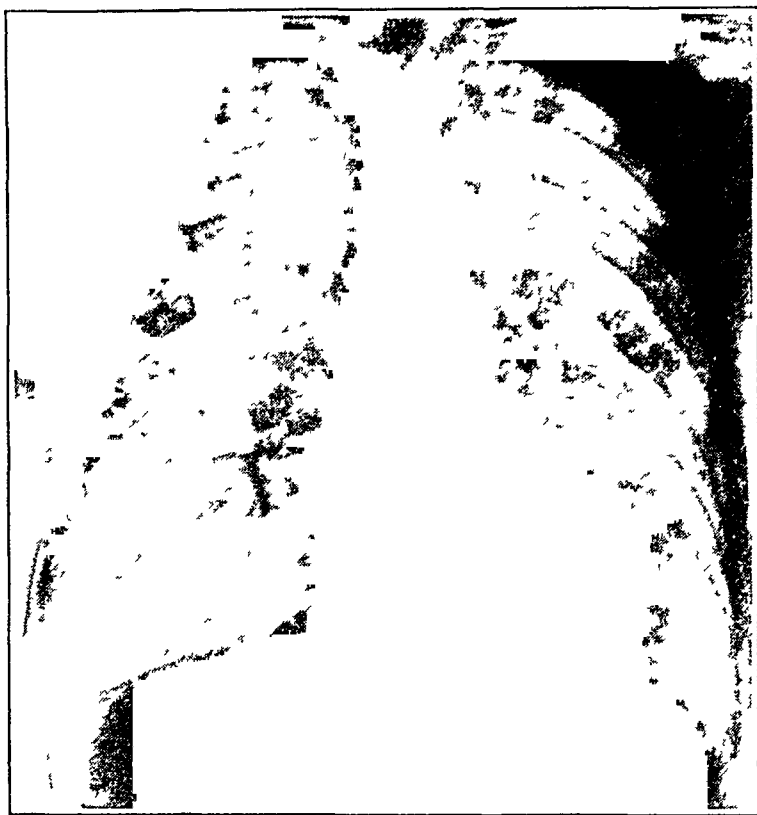


Fig. 3 (case 4)—Aneurysmal bulge on the left border slightly below the middle

revealed a thin man with slight cyanosis of the lips. There was marked generalized arteriosclerosis. The pulse was regular, at a rate of 88. The blood pressure was 132 systolic and 82 diastolic. There was a diffuse forcible pulsation in the region of the fourth, fifth and sixth interspaces. It was maximum in the fifth space but covered a wide area, extending as far as the midaxillary line at the level of the fifth interspace. No thrill was felt over the pulsation. The heart sounds over the pulsation were of fairly good quality, but at the base of the heart they were faint. There was a systolic murmur over the pulsation. Gallop rhythm was not present. There were bilateral basal rales in the lungs. The liver was not enlarged. There was weakness of the left leg, and a Babinski sign could be elicited on this side. The Wassermann reaction was negative. The electrocardiogram showed a negative T wave in lead I. In lead IV the R wave was absent, the S wave was slurred and the RS-T segment was elevated, being followed by a slightly negative T wave. Roentgen examination showed calcification of the aorta and a localized bulge just above the apex. The heart was not significantly enlarged. Fluoroscopic examination showed a marked saccular dilatation of the left ventricular wall, just above the apex. There was a vigorous pulsation in this area, and the pulsations were opposite to those of the rest of the ventricle. The patient was discharged, improved.



blood pressure was 132 systolic and 92 diastolic. There was a marked visible pulsation over the lower portion of the precordium between the sternum and the nipple. No thrill was felt. There was a soft systolic murmur at the apex. With each heart beat a clicking sound was also heard in the region of the apex. The results of physical examination were otherwise normal, as were those of laboratory studies. The Wassermann reaction was negative. The electrocardiogram showed a negative T wave in lead I and an almost absent R wave in lead IV (right arm wire connected to precordial electrode and left leg wire to left leg electrode). A roentgenogram showed a localized bulge about the midportion of the left border of the heart. Fluoroscopic and roentgenkymographic examinations showed systolic expansion in the region of the bulge. A diagnosis of aneurysm of the heart was made. The patient continued to be active with no particular complaints. While playing in a school playground on Aug 28, 1940, she suddenly fell over, dead. Autopsy showed a heart of normal size. Projecting from the septum of the mitral ring between the auricle and ventricle directly beneath the posterior cusp of the mitral valve was a multiloculated sac, measuring 5 by 7 cm. This consisted of dense fibrous tissue in which on microscopic examination strands of heart muscle were seen.



Fig 2 (case 2) —Aneurysmal bulge in the midportion of the left border

The adjacent auricular and ventricular muscle was normal except for the presence of recent Aschoff bodies. There were no old rheumatic lesions, and the coronary vessels were normal.

CASE 3—J S., a Negro aged 46, was admitted to Kings County Hospital on Sept 22, 1937. Ten days before admission he had been stabbed over the heart. He did not faint, vomit or spit up blood. He continued to work for six days, and then dyspnea, cough and edema of the ankles developed, which gradually increased. Previous to this the patient had always been in good health. On physical examination he was suffering from orthopnea and cough. There was marked bilateral distention of the veins of the neck. The pulse was regular, at a rate of 88 beats per minute, and the blood pressure was 140 systolic and 100 diastolic. There was evidence of the stab wound in the fourth interspace over the cardiac area. The heart was slightly enlarged to the left. A systolic thrill extending from the third interspace to the sternum was felt, and a harsh systolic murmur was heard in the same region. There was no abnormal pulsation noticed. The lungs were filled with dry and moist rales, and the liver was enlarged 3 fingerbreadths. There was marked edema. The Wassermann reaction was 4 plus. The electrocardiogram showed negative T waves in leads II and III. On roentgen examination only some enlargement of the left ventricle was seen. On the following day the temperature rose to 101 F and the pulse rate to 100 beats per minute. After this the

admission he had suffered intermittent precordial pain. On the day of admission he was seized with extremely severe pain in the chest, which did not abate. Physical examination showed a man in severe pain. The heart rate was 96 beats per minute, and the blood pressure was 162 systolic and 90 diastolic. The heart did not appear enlarged, and there was a soft systolic murmur at the apex. The Wassermann reaction was negative. The electrocardiogram showed a typical coronary occlusion of the  $Q_1 T_1$  type. The patient made a satisfactory recovery and was discharged on March 11, 1941. He was readmitted on September 15. He stated that he had had no precordial pain since discharge but had suffered from increasing dyspnea on exertion, which had been worse in the last week, otherwise, he had no complaints. On physical examination there was generalized arteriosclerosis. The pulse rate was 72 beats per minute, and the blood pressure was 154 systolic and 94 diastolic. The apex was clearly visible in the sixth interspace in the anterior axillary line. Above and separate from this, over a wide area in the fourth and fifth interspaces, extending as far as the mid-axillary line, there was a diffuse pulsation. This seemed to start before and to last longer than the apical thrust. There was no thrill felt. The heart sounds were good. A systolic murmur



Fig 5 (case 6) —Angulation of the left border. The aneurysm was shown by fluoroscopic and roentgenokymographic study to be in the region of the flattened area.

was heard at the apex, but this was less intense over the upper pulsation. There was a faint systolic murmur at the aortic area. There were some dry rales at the base of each lung. The electrocardiogram was similar to that on discharge previously. The roentgenogram showed angulation of the left border, the lower part being flat. In this area on fluoroscopic examination there was seen some bulging during systole, but the pulsations were diminished. This was confirmed by roentgenokymographic examination. After a short stay the patient was discharged much improved.

CASE 7—M. M., a white man aged 59, was admitted to the Brooklyn Jewish Hospital on May 20, 1936. He suffered from acute coronary occlusion, the electrocardiograms being of the  $Q_3 T_3$  type. He improved satisfactorily and was discharged on July 21. Immediately after this he took a considerable amount of exercise one day and on returning home had severe dyspnea and dull precordial pain. He was readmitted to the Jewish Hospital on July 23. The pulse rate was 120, and the blood pressure was 140 systolic and 80 diastolic. The heart was enlarged to the left, and there was a marked diffuse heaving over the entire precordium. The heart sounds were faint and a systolic murmur was present at the aortic area. There was

CASE 5—J. C., a Negro aged 43, was admitted to Kings County Hospital on May 28, 1937, complaining of dyspnea and of swelling of the legs and abdomen. The former had been present for a long time, but the latter had developed recently. There was a history of rheumatic fever at the age of 15. Physical examination showed some distention of the veins in the neck and considerable edema. The pulse rate was 90 beats per minute, and the blood pressure was 140 systolic and 100 diastolic. The heart was considerably enlarged, but there were no murmurs and the heart sounds were good. There were rales at the bases of both lungs, and the liver was enlarged 4 fingerbreadths. The Wassermann reaction was 4 plus. The electrocardiogram showed slurring of the QRS segment in all leads and a negative T wave in lead I. A roentgenogram was not taken at this time. The patient was discharged after the heart failure was relieved. He was readmitted on March 20, 1939, suffering from acute bronchopneumonia, from which he recovered. On May 9 and October 27 he returned with heart failure and had similar physical findings. On the latter admission roentgen examination revealed a heart which was enlarged to the left. About halfway on the left ventricular contour there was angulation, and below this, flattening of the wall. Roentgenokymographic examination showed systolic expan-



Fig. 4 (case 5)—Angulation of the left border of the heart. The aneurysm was proved by autopsy to be in the lower part of the anterior wall of the left ventricle and apex, the flattened area.

sion in this region. In December he suffered from an attack of hemiplegia of the left side, from which he made a satisfactory recovery. He was readmitted on Jan. 26, 1940, again with heart failure. The final admission was March 3, 1941, for the same complaints. The only significant changes which had taken place were that the electrocardiogram now showed left bundle branch block and the blood pressure was 170 systolic and 120 diastolic. On March 7 pain developed in the suprapubic region and nausea but there was no vomiting. There was tenderness in this region and some rigidity. Shortly after this he died. Autopsy revealed a heart which was considerably enlarged. There was concentric hypertrophy of the left ventricle. The apex was replaced by fibrous tissue, and there was an aneurysmal dilatation in this region. The coronary vessels were markedly sclerotic, but no occlusion was found. Cardiac cirrhosis of the liver was present and an old thrombus in the right femoral artery. Death was due to mesenteric thrombosis with peritonitis.

CASE 6—A. D., a white man aged 58, was admitted to Kings County Hospital on Jan. 22, 1941. He stated that he had had high blood pressure for a long time. Seven days before

antemortem thrombus. There were an old occlusion of the anterior descending branch of the left coronary artery and severe generalized coronary sclerosis. There was no evidence of recent infarction. Generalized arteriosclerosis was found, and there was blood-tinged fluid in the right pleural cavity. The liver was enlarged 3 fingerbreadths.

CASE 9—C G, a white man aged 55, entered Long Island College Hospital on Jan 6, 1934. He stated that until three weeks before he had never been sick. At this time he noticed edema of the ankles in the evening. After a week the swelling had extended farther up the legs. At about the same time he noticed pain of a gripping nature on both sides of the chest radiating to the left shoulder. The pain was not related to exercise. He also began to cough and had chilly sensations. He suffered from shortness of breath, which became progressively worse. The night before his admission nocturnal dyspnea was present, accompanied by precordial pain. The temperature on admission was 100.4 F, and the pulse was regular at a rate of 84 beats per minute. The blood pressure was 110 systolic and 80 diastolic. There was cyanosis of the lips and extremities and edema of the legs. The heart was enlarged downward and to the left. A systolic crunching sound was present in the midprecordium. There were no murmurs. There were an impaired percussion note at both bases and many rales on both sides. The liver was enlarged 2 fingerbreadths. The Wassermann reaction was negative. The electrocardiogram showed evidence of coronary occlusion. On roentgen examination, the heart was seen to be enlarged in all diameters, and there was calcification of the aorta. On the patient's second day in the hospital tachycardia at rate of 150 beats per minute developed. He was given digitalis and quinidine, and the next day the previous rate was resumed. On January 15 auricular fibrillation was observed but his general condition had improved. The fibrillation continued, but then he commenced to lose ground. On January 30 a strong irregular cardiac impulse was seen and felt between the ribs and iliac crest. He was stuporous and died that evening. Autopsy revealed a considerably enlarged heart. The pericardium was adherent to the apex. The lower segment of the left ventricle was the seat of a large aneurysm, and there were old and recent infarctions in this area. There was an adherent thrombus in the region of the aneurysm. An old occlusion of the left anterior descending artery was present, and sclerosis of the other coronary vessels. An embolus was present in the left cerebral artery.

CASE 10—H A, a white man aged 71, was admitted to Long Island College Hospital on Dec 18, 1939. He stated that for about eight years he had suffered from bronchitis with cough and sputum. He was dyspneic for about three to four years and had some edema of the ankles for three months. Physical examination showed a slightly dyspneic man. The pulse was regular in rhythm, at a rate of 80 beats per minute, and the blood pressure was 92 systolic and 64 diastolic. The heart was considerably enlarged, the apex being in the anterior axillary line. There were a short systolic murmur at the apex and a rough systolic murmur at the aortic area. There were scattered dry rales in the lungs, and the edge of the liver was just palpable. The Wassermann reaction was negative. The electrocardiogram showed changes suggestive of an old anterior infarct. The patient was discharged on December 31 much improved. He was readmitted on May 24, 1941. He had been comparatively well since discharge until two weeks before, when congestive heart failure again developed. At this time the pulse rate was 104 beats per minute and the apex was in the midaxillary line. There were many moist rales in both lungs. The liver was enlarged 4 fingerbreadths. His condition became progressively worse, and he died the next day. Autopsy showed a considerably enlarged heart. In the region of the apex and the anterior wall along the septum there was an aneurysmal dilatation about the size of a child's fist. It contained antemortem thrombus, and the pericardium was adherent in this area. There was an old occlusion of the anterior descending branch about the junction of the upper and middle thirds. The rest of the coronary vessels showed moderate sclerosis.

CASE 11—E T, a white man aged 77, was admitted on Oct 30, 1932 to the ear, nose and throat service of Long Island College Hospital, suffering from acute suppurative mastoiditis. The pulse rate was 78 beats per minute and the temperature 100 F. The blood pressure was 158 systolic and 92 diastolic. The heart was not significantly enlarged. There was a harsh systolic murmur at the apex and a softer systolic murmur at the aortic area. The results of physical examination were otherwise normal. The Wassermann reaction was negative. The mastoid condition became progressively worse, and on November 2 an operation was performed. The condition continued to deteriorate, and the patient died on November 7. Autopsy revealed some enlargement of the heart. On the posterior surface of the left ventricle, close to the region of the mitral valve, there was a calcified aneurysm of the left ventricle. The sac contained no antemortem clot. There was calcification of the aortic valve, with stenosis. The anterior descending artery showed calcification and was narrowed 1 cm from its origin. There was moderate sclerosis of the right coronary artery. There were two aneurysms of the aorta near the origin of the iliac vessels, measuring, respectively 5 by 7 cm and 5 by 6 cm. The right kidney was atrophied.

evidence of fluid in both pleural cavities. The patient was transferred to Kings County Hospital on July 30. The pulse rate had fallen to 80, and the blood pressure was 150 systolic and 90 diastolic. The apex was in the sixth space, 1 inch (2.5 cm) outside the midclavicular line. The heart sounds were faint. There were moist rales at the bases of the lungs, but the fluid in the pleural cavities had disappeared. Roentgen examination showed an angulation of the left border of the heart with suggested myomalacia in the lower part of the left ventricle and apex. Fluoroscopic examination showed diminished pulsation in this region with some systolic expansion, and kymographic studies confirmed this. The Wassermann reaction was negative. The patient was discharged after he recovered from the attack but was readmitted on September 30, with the same symptoms. At this time the diffuse pulsation which had been noted over the whole precordium seemed to be most pronounced at the apex. On October 3 the electrocardiogram suggested that he had had a recent, as well as an old, infarction. The patient remained free from signs of decompensation while at rest, but any activity brought on heart failure. He was transferred to the Jewish Home for Incurables, where he died this summer. An autopsy was not obtained.



Fig 6 (case 7) —Angulation of the left border. The aneurysm was demonstrated by fluoroscopic and roentgenkymographic study to be in the region of the flattened area.

CASE 8—J. K., a white man aged 62, was admitted to Kings County Hospital on Aug 20, 1937. He stated that two weeks before, while he was eating, severe abdominal pain suddenly developed. This was situated near the umbilicus and radiated to the left upper quadrant. There were no gastrointestinal symptoms except that he had had diarrhea for two days. He also suffered from some dyspnea. He continued to work, but the pain and dyspnea continued. The pain was most severe when he lay down. The condition grew progressively worse so he came to the hospital. Physical examination showed pronounced orthopnea. The respiratory rate was 40 per minute. The veins in the neck were distended. The pulse was weak, but the rhythm was regular, at a rate of 115 beats per minute. The blood pressure was 184 systolic and 112 diastolic. The heart was enlarged to the left, and the heart sounds were faint. No murmurs were heard. There were bilateral basal rales, and the liver was enlarged 3 fingerbreadths. The electrocardiogram suggested an acute coronary occlusion with the infarct in the anterior wall of the left ventricle. Roentgen examination showed generalized enlargement of the heart with dilatation of the aorta. The Wassermann reaction was negative. On November 3 he had what appeared to be a cerebral embolus, and a week later he died. Autopsy showed a considerably enlarged heart. The pericardium was adherent to the left ventricle. In the region of the apex there was an aneurysm 8 cm in diameter filled with

## CLINICAL FEATURES

*Site*—Most aneurysms occur in the left ventricle, as is to be expected since myocardial infarction of the right ventricle is uncommon. The most frequent site is the apex and its immediate vicinity, and the artery which has been most often occluded is the anterior descending branch of the left coronary artery. In 9 cases of the present series the aneurysm was located in the region of the apex: in 3, higher on the anterior or lateral wall, and in 1, on the posterior wall.

*Symptoms*—There are no symptoms characteristic of aneurysm of the heart, indeed, the patient may be able to carry on ordinary activity without discomfort and the aneurysm may be discovered during the course of a routine examination (case 2). The most common symptoms are those associated with congestive heart failure, although in some instances angina pectoris may be the sole complaint.

*Physical Signs*—The most important physical sign is the presence of abnormal pulsation in the precordial area. It is stated that a displaced apex which is more diffuse than normal and both forceful and heaving is characteristic. This is, however, frequently seen in large hearts without aneurysm and would be valuable only if the possibility of aneurysm were considered as a result of other evidence. It was seen in 2 cases in the present series. Libman and Sacks,<sup>9</sup> Libman<sup>10</sup> and Diessler and Pfeiffer<sup>11</sup> stressed the value of a pulsation separate and distinct from the apex, especially when it is situated above the fifth rib. This is a most important sign, and its presence frequently permits the diagnosis to be made by physical examination alone. It was seen in 5 of my cases. Sometimes the abnormal pulsation appeared before the apical thrust and lasted longer. A muffling of the heart sounds or a disproportion between the forcefulness of the pulsation and the intensity of the heart sounds has been described. This was found in only 3 of my patients. Some had heart failure and might have shown it without aneurysm. Furthermore, the heart sounds are often diminished after coronary occlusion even when no aneurysm is present. Gallop rhythm has been noted in the literature but was not noted in these cases. It also may be evidence of myocardial failure and is not characteristic of aneurysm. Lutembacher<sup>12</sup> stressed the value of pain over the apex. This was found in 1 of my patients but does not seem to be a sign of any particular value. Percussion demonstrates only a very large aneurysm and has been superseded by roentgen examination. Murmurs do not aid in the diagnosis. A systolic murmur is often present, and 1 of my patients had a double murmur over the abnormal pulsation. The blood pressure was not significantly elevated except in 1 instance. Congestive heart failure was present at some time in 9 of my cases and is the common cause of death.

## ROENTGENOLOGIC OBSERVATIONS

The most valuable information is obtained by fluoroscopic examination, because one can study not only the cardiac contour from all angles but the pulsations as well. Roentgenograms should be taken for detailed analysis not only in the posteroanterior position but in the oblique position, the most favorable position having been determined by fluoroscopic study. Certain aneurysms of the anterior wall and those on the posterior wall can be seen only in roentgenograms taken with the patient in the oblique position. By roentgenokymographic examination

9 Libman, E, and Sacks, B. *Am Heart J* **2** 321, 1927.

10 Libman, E. *Proc Interstate Post-Grad M A North America* (1926), 1927, p. 60.

11 Diessler, W, and Pfeiffer, R. *Ann Int Med* **14** 100, 1940.

12 Lutembacher, R. *Arch d mal du cœur* **13** 49, 1920.

CASE 12—R S, a white woman aged 58, was admitted to Kings County Hospital on Dec 19, 1938. One week before, severe precordial pain radiating down the left arm and dyspnea had developed. This improved, but the pain again returned severely the day before admission. Physical examination revealed a woman suffering from some dyspnea. The temperature was 100 F, and the pulse was regular in rhythm, at a rate of 115 beats per minute. The blood pressure was 130 systolic and 74 diastolic. The heart was enlarged to the left, and there were systolic murmurs at the apex and aortic areas. The lungs were normal, and the liver was not enlarged. The Wassermann reaction was negative. The electrocardiogram showed a QRS segment of low voltage in all the standard leads, the R wave was almost absent, and there was an elevated RS-T segment in lead IV, suggesting an acute infarction of the anterior wall. No roentgenogram was taken. The condition progressed satisfactorily, but on December 29 the patient suddenly became comatose. Her pulse became irregular, and she died soon after. Autopsy showed an enlarged and dilated heart. On the anterior surface of the left ventricle at the apex there was a large gray-white aneurysmal bulge, to which the pericardium was adherent. There were marked coronary sclerosis and arteriosclerosis of the aorta. Acute pancreatitis was present.

CASE 13—J T, a white man aged 53, was admitted to Kings County Hospital on April 25, 1941. His condition was so serious that no history could be obtained. The temperature was 106 F, and the respiratory rate was 44. The blood pressure could not be obtained. Extreme enlargement of the right cervical glands was present. The heart was totally irregular, at a rate of about 140 beats per minute. It was enlarged, and the heart sounds were weak. No murmurs were heard. The lungs were normal, and the liver was not enlarged. The Wassermann reaction was negative. A bedside roentgenogram was taken and apart from cardiac enlargement showed nothing significant. An electrocardiogram was not obtained. The patient died soon after admission. Autopsy revealed considerable cardiac enlargement. The pericardium was adherent to the lower half of the left ventricle. At the apex there was an aneurysmal dilatation, 6 by 5 cm. The wall was hard and calcified, and there was no evidence of muscle in this region. The aortic and mitral valves were sclerotic. The coronary arteries were very sclerotic, but no occlusion was found. Marked generalized arteriosclerosis was present.

#### ETIOLOGY

All authors agree that in the majority of cases cardiac aneurysm follows coronary occlusion. Steinberg<sup>1</sup> stated that in 84.8 per cent of the 207 cases which he analyzed cardiac aneurysm followed coronary occlusion. In 13 of the 16 cases of Parkinson, Bedford and Thomson<sup>2</sup> there was a previous coronary occlusion. The evidence of coronary occlusion consists of either a typical history or positive electrocardiographic signs or both. In 8 of the present series of cases there were the characteristic signs of a previous occlusion. Cases have been described in which in patients with infective endocarditis the aneurysm followed abscesses of the ventricular wall caused by infected emboli. A few cases have been described in which the cardiac aneurysm was secondary to gummas of the ventricle. Two patients in the present series who had no evidence of a previous coronary occlusion had a positive Wassermann reaction, but postmortem examination of 1 showed no syphilitic lesions in the heart muscle while in the other the aneurysm was secondary to trauma. Congenital aneurysms have been reported in rare instances. These have mainly involved the pars membranacea septi. In 1 of the aforementioned cases the aneurysm, projecting from the ventricular wall, was of congenital origin. Trauma of the heart is sometimes followed by aneurysm and was the cause in 1 of this series. Necrosis of the myocardium secondary to rheumatic lesions has been stated to be an etiologic factor but must be very infrequent. In 1 case of undetermined origin there was a history of rheumatic fever at the age of 15 but the autopsy gave no evidence that this played any part, no satisfactory cause could be determined.

A summary of the literature shows that 66 per cent of the patients with this condition are males. In the present group there were 11 men and 2 women.

the extent of the recovery which ensued and how much the patient was able to accomplish despite the presence of an aneurysm. Indeed, in case 2 (congenital aneurysm) there were no cardiac symptoms at all. This feature has been commented on by other authors. The aneurysm itself does not seem to play a great part in determining the outcome in most instances; the deciding factor seems to be the functional capacity of the rest of the ventricle. Rupture of the heart was not a cause of death in any of my cases. The usual termination is progressive cardiac decompensation. In some instances fatal embolization takes place.

#### DIFFERENTIAL DIAGNOSIS

1 *Tumor of the Heart*—As in aneurysm, this may cause a bulge on the cardiac contour. If the tumor is metastatic, there may be evidence of carcinoma elsewhere, while there is, as a rule, no evidence of a previous coronary occlusion. With a tumor the heart is not enlarged usually, whereas with an aneurysm this is common. The pulsation in a solid tumor is synchronous with the rest of the heart, whereas in an aneurysm there is usually systolic expansion or absent pulsation. In a soft tumor, such as a very vascular sarcoma or a hemangioma, a reversal of pulsation may take place. Fulton<sup>16</sup> described a case of systolic expansion which responded well to antisiphilitic therapy.

2 *Aneurysm of a Sinus of Valsalva*—This may project to the left and upward and thus cause difficulty. A positive Wassermann reaction or aortic insufficiency would suggest this as a likely diagnosis.

3 *Aneurysm of a Coronary Artery*—This type of aneurysm is rare and seldom large. If it reaches a sufficient size to be easily seen, it may readily be mistaken for an aneurysm of the heart.

4 *Aneurysm of the Descending Aorta*—This condition may be seen projecting to the left of the cardiac contour, but careful roentgenologic study will easily establish the correct diagnosis.

5 *Diverticulum of the Pericardium, Loculated Pericardial Effusion or Cyst of the Pericardium*—Any of these conditions may resemble aneurysm. Cushing<sup>17</sup> found on a review of the literature that the first in most instances was seen on the right side, where aneurysms are not common, and he also stated the belief that a change in shape of the shadow on respiration is an important diagnostic feature. The history of a previous pericarditis may help in differentiating effusion, and the type of pulsation seen in aneurysm may be an aid. Differences in density of the roentgenographic shadow between the heart and the pericardial disease may at times help to settle the matter.

6 *Enlarged Pulmonary Conus*—An enlarged pulmonary conus secondary to mitral stenosis, congenital heart disease, cor pulmonale or Ayerza's disease should give little difficulty in differential diagnosis, as in these the results of roentgenographic examination rarely simulate aneurysm and the clinical features of these diseases are characteristic.

7 *Tumors of the Chest*—Tumors of the mediastinum or of the lung can be separated by careful roentgenologic study and the clinical features of pressure in the mediastinum or evidence of pulmonary disease.

8 *Para-Apical Pad of Fat*—The para-apical pad of fat is easily differentiated from an apical aneurysm by roentgen examination.

16 Fulton, M. N. Aneurysm of the Ventricle of the Heart, J. A. M. A. **116** 115 (Jan. 11) 1941.

17 Cushing, E. H. Diverticulum of Pericardium, Arch. Int. Med. **59** 56 (Jan.) 1937.



one is enabled to study the pulsations in detail. Studies after the injection of diodast may demonstrate the aneurysm clearly if it is not filled with thrombus.

Parkinson, Bedford and Thomson<sup>5</sup> described the following signs as the most important aids in establishing the diagnosis by roentgenography: (1) enlargement of the left ventricle with deformity of its contour, (2) a localized protuberance inseparable from the shadow of the heart on rotation of the patient, (3) abnormal or absent pulsation of the aneurysmal zone, (4) evidence of adhesions between the heart and the wall of the chest or the diaphragm and (5) calcification of the wall of the sac or its contained clot. They particularly stressed the value of an abrupt ledging of the anterior contour of the heart as seen with the patient in the right oblique position. Aneurysms of the posterior wall are demonstrated with the patient in the left oblique position and sometimes cause displacement of the esophagus.

Three of the patients in the present series had no roentgen examination, as cardiac aneurysm had not been suspected clinically. Eight showed enlargement of the heart and 3 a localized bulge. Angulation of the left ventricular contour was seen 3 times. Abnormal pulsations demonstrated by fluoroscopic or roentgenokymographic examination are frequently of the greatest value. Their character varies from a reversal of the normal type to absent pulsation. Schwedel and Gross<sup>13</sup> stated that in their cases the pulsations were synchronous, asynchronous, systolic or contrapulsile. The pulsations were proved to be abnormal in the aneurysmal zone in 6 of my patients. Of these 4 showed an expansion during systole of the rest of the ventricle, with ballooning out in a most striking manner in 2 of them, the other 2 had very small or no pulsations. In none were pulsations of the normal type. Gross and Schwedel<sup>14</sup> have emphasized the value of localized pericardial adhesions in the diagnosis. This was not present in any of my cases, but on autopsy adhesions of the pericardium to the sac were seen in 6, they were absent in 1, and in 2 there was no note as to its presence or absence. None of the patients in this study showed calcification of the wall of the sac or of a thrombus contained therein. When calcification is seen it must be differentiated from calcification of the pericardium. The latter is on the surface and usually more diffuse, while in calcification of an aneurysm the calcification should be localized and not confined to the surface.

#### ELECTROCARDIOGRAPHY

Ehler and Konigsberg<sup>15</sup> described electrocardiographic signs which they considered of diagnostic value in cases of cardiac aneurysm. In none of my cases were there changes of this type. Electrocardiograms were of help only when they established the existence of a previous coronary occlusion.

#### PROGNOSIS

Cardiac aneurysm indicates, as a rule, very extensive damage to the ventricle. It has been suggested that aneurysm is more likely to develop when an adequate period of rest has not followed the coronary occlusion. This seems a reasonable expectation, but at least several of my patients were known to have received very satisfactory treatment of the occlusion. Nine of them had heart failure at some time during their course. However, it was surprising in many instances to observe

13 Schwedel, J. B., and Gross, H. *Am J Roentgenol* **41** 32, 1939.

14 Gross, H., and Schwedel, J. B. *New York State J Med* **41** 488, 1941.

15 Ehler, M., and Konigsberg, J. *Electrocardiographic Findings in Cases of Ventricular Aneurysm*, *Arch Int Med* **64** 493 (Sept.) 1939.

common conditions, that it is very doubtful whether a satisfactory differentiation can be made. Zdansky<sup>23</sup> points out that aneurysm must attain a considerable size before a clearly circumscribed bulging at the apex is seen. The apex region can be studied in more detail during very deep inspiration or after inflation of the stomach with gas. Aneurysms higher in the ventricular wall or on the posterior wall, the latter being usually basal, can be visualized much more readily.

#### CONCLUSIONS

1 There are no symptoms characteristic of aneurysm of the heart. It may be asymptomatic, but as a rule some symptoms due to congestive heart failure are present. Sometimes angina pectoris is the only complaint.

2 The signs which are most frequently present and appear to be most important in the diagnosis of aneurysm of the heart are (a) a history or electrocardiographic proof of previous coronary occlusion, (b) the presence of an abnormal precordial pulsation distinctly separated from the apex pulsation, particularly when it is situated above the fifth rib, (c) on roentgen examination a localized bulge which cannot be separated from the heart shadow in any view in which it can be seen or an angulation of the left border of the heart, (d) systolic expansion in the region of the abnormality as seen on fluoroscopic or roentgenokymographic examination, which is practically conclusive evidence, and small contractions or none in this area, which are strongly suggestive, (e) localized pericardial adhesions or calcification of the aneurysmal wall or its contents.

3 The following conditions simulate aneurysm of the heart most closely and must be carefully differentiated from it: (a) tumor of the heart, (b) aneurysm of a sinus of Valsalva, (c) aneurysm of a coronary artery, (d) calcification of the pericardium, (e) diverticulum of the pericardium, (f) loculated pericardial effusion, (g) cyst of the pericardium.

The physicians of Kings County and Long Island College hospitals who had some of the patients reported on under their care at different times gave permission to include their cases in the series. The physicians of Brooklyn Hospital gave permission to use the data for the patient admitted to that institution (case 1).

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<sup>23</sup> Zdansky, E. Röntgendiagnostik des Herzens und der grossen Gefässe, Berlin, Julius Springer, 1939.

## COMMENT

One of the most striking features noted in reviewing the literature is the marked increase in the incidence of cardiac aneurysm in recent years compared to the incidence in earlier reports. These were based on autopsy studies, hence it seems that the condition was unlikely to have been overlooked. In 1884 Legg<sup>18</sup> observed only 3 instances in 1,890 autopsies. Summaries of large series of post-mortem studies showed as low, if not a lower, incidence. In contrast, Parkinson, Bedford and Thomson,<sup>19</sup> combining their own statistics with those of other authors reporting its occurrence after coronary occlusion, stated that cardiac aneurysm takes place in 9 per cent. Coronary occlusion was not usually recognized before its description by Herrick<sup>19</sup> in 1912, hence it is difficult to say whether or not there has been an increase in its incidence. However, there is such a marked discrepancy that such would hardly account for the difference. The most likely explanation is that the earlier authors considered as instances of aneurysm only those cases in which there was a definite bulging of the ventricle beyond the general contour of the heart whereas of late less marked changes have been so diagnosed. Even small indentations of the endocardial wall at the site of an old infarct when the epicardial surface was not involved have been reported as aneurysms in some series. This seems hardly warranted. If such are to be included one would say that in most instances where an area of myomalacia is present an aneurysm exists. Gubner and Crawford,<sup>20</sup> by roentgenokymographic examination, demonstrated that systolic expansion of the infarcted area takes place in a large percentage of cases of coronary occlusion. Similar observations have been reported after fluoroscopic study by Master, Gubner, Dack and Jaffe.<sup>21</sup> It would seem better to confine the term "cardiac aneurysm" to a permanent localized bulging or, during systole a well marked localized expansion beyond the contour of the rest of the heart. On fluoroscopic examination one sometimes sees a localized bulging of the wall during systole which during diastole collapses so that the wall of the heart is flattened. Christian and Frik<sup>22</sup> reported such a case. The diagnosis was made by roentgen examination, but the aneurysm was incorrectly located, as autopsy revealed that what had been thought to be the aneurysm was the normal part of the ventricle. Figures 4, 5 and 6 illustrate this condition, while figures 1, 2 and 3 show permanent localized bulging. In considering the pulsations of the ventricle one would expect that every instance in which a large part of the myocardium has been damaged would show bulging during systole with marked reversal of pulsation. The reason for this not being so is that it may be prevented by mural thrombi, reinforcement by strong pericardial adhesions or by calcification.

There is no doubt that roentgen examination is the most important aid in the diagnosis of cardiac aneurysm, as changes in the contour can be, as a rule, clearly delineated. Unfortunately, the most common site for aneurysm is the apex, which is the position in which the contour can be studied least effectively. At this point the heart and diaphragmatic shadows mingle, which tends to obscure deformities of the cardiac contour. A diffuse concentric apex rounding or a broadened blunted apex has been stated to be characteristic. These are, however, so frequently seen in patients suffering from hypertension or aortic insufficiency, which are relatively

18 Legg, J. W. *Some Account of Cardiac Aneurysms*, London, J. & A. Churchill, 1884.

19 Herrick, J. B. *Clinical Features of Sudden Obstruction of the Coronary Arteries*, J. A. M. A. **59** 2015 (Dec 7) 1912.

20 Gubner, R., and Crawford, J. H. *Am Heart J* **18** 8, 1939.

21 Master, A. M., Gubner, R., Dack, S., and Jaffe, H. L. *Proc Soc Exper Biol & Med* **41** 89, 1939.

22 Christian and Frik. *Klin Wchnschr* **1** 582, 1922.

materials. A few observers have discussed the importance of the enterococci in general terms,<sup>6</sup> but they have presented few specific clinical data. It is now particularly important that the clinical significance of the enterococci be established, since these organisms have been repeatedly shown to be almost completely resistant to the bacteriostatic action of sulfonamide compounds.<sup>7</sup> The use of these agents in infections caused by fecal streptococci may not be followed by a satisfactory clinical result.

A study was therefore undertaken in this clinic of hemolytic and nonhemolytic streptococci isolated from human clinical materials, modern clinical and biologic methods being applied in their classification. The detailed results of these observations have been described elsewhere.<sup>8</sup> Of great interest was the fact that nearly one half of the streptococci recovered from sources other than the respiratory tract were enterococci.

It is the purpose of this paper to describe the disease processes from which these streptococci were isolated, to discuss the results of chemotherapy and to define, in general, the place of the enterococci in clinical medicine.

#### IDENTIFICATION OF THE ENTEROCOCCI

The enterococci occur in the tissues and in culture as lancet-shaped, gram-positive cocci, usually in pairs or very short chains. They resemble pneumococci so closely in appearance that special studies are necessary to differentiate them. In liquid mediums growth is very rapid and diffuse. On blood agar plates the colonies are large, flat, smooth and gray. Beta hemolysis will frequently be present, although the typical *Str. faecalis* is entirely nonhemolytic.

The important biologic characteristics, as described by Sherman,<sup>5a</sup> which permit the identification of the enterococci are the ability of these bacteria to grow well at 10 C and 45 C in the presence of 6.5 per cent sodium chloride, 0.1 per cent methylene blue and a  $p_H$  of 9.6 and to resist heating for thirty minutes at 60 C. The last-mentioned qualification has been most widely applied in the past and is now known to be inadequate for the differentiation of the fecal from other kinds of streptococci.

Practically all of the streptococci which fulfil these biologic requirements will be found serologically to be members of the Lancefield group D. Approximately 25 per cent of the strains isolated from human sources will be hemolytic, and 10 per cent will be found to liquefy gelatin. For the purpose of clinical investigation it is most profitable to consider the hemolytic, nonhemolytic and proteolytic strains as members of a very closely related group of streptococci rather than as separate species, since no difference in the type of disease process caused by each variety has been demonstrated.

The technical and statistical details of the biologic and serologic classification of the streptococci have been described elsewhere.<sup>8</sup> From these observations it appears that a streptococcus which grows well in 6.5 per cent sodium chloride broth and in milk containing 0.1 per cent methylene blue may be safely classified

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6 Houston, T. Enterococci. Proc. Second Internat. Cong. Microbiol., 1936, p. 141.  
Aschoff, L. Ueber den Enterokokkus (*Streptococcus* Libman), in Contributions to the Medical Sciences in Honor of Dr. Emanuel Libman by His Pupils, Friends and Colleagues, New York, International Press, 1932, vol. 1, p. 87.

7 Neter, E. (a) The Bacteriostatic Action of Sulfanilamide upon Hemolytic and Non-Hemolytic Enterococci, *J. Bact.* **40**: 383, 1940; (b) Experimental Observations on Bacteriostatic Action of Sulfanilamide and Related Compounds upon Enterococci, with Particular Reference to Strains Isolated from Urinary Tract Infections, *J. Urol.* **45**: 241, 1941.

8 Rantz, L. A. The Serological and Biological Classification of Streptococci from Human Sources, *J. Infect. Dis.* **71**: 68 (1942).

# ENTEROCOCCIC INFECTIONS

AN EVALUATION OF THE IMPORTANCE OF FECAL STREPTOCOCCI AND  
RELATED ORGANISMS IN THE CAUSATION OF HUMAN DISEASE

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That streptococci having distinctive properties are normally present in the contents of the human bowel and that these organisms may at times be the etiologic agents of infectious processes in man was first emphasized by Andrewes and Horder<sup>1</sup> in 1906, who applied the descriptive term *Streptococcus faecalis* to them. Since that time a considerable literature has grown up dealing with various aspects of the classification of the fecal streptococci and organisms closely related to them, all of which have come to be included in a loosely defined group the enterococci.

Very recently the development by Lancefield<sup>2</sup> of a precipitin technic has permitted a more satisfactory classification of the hemolytic streptococci than had previously been possible and it is now known that nearly all serious human infections, particularly those of the respiratory tract, are caused by members of her group A.

Sherman has demonstrated that most of the streptococci of the human bowel<sup>3</sup> are serologically homogenous and are members of the Lancefield group D. Furthermore, he has described biologic tests<sup>4</sup> which permit the satisfactory classification of these streptococci in the absence of serologic studies and has pointed out that both hemolytic and nonhemolytic varieties occur which are serologically and biologically identical.

In the light of these recent important observations, the interpretation of the earlier work on the fecal streptococci becomes difficult, since many of the differential tests used are now known to be unreliable. This is especially true in relation to organisms isolated from and described as the etiologic agents in human infections. For this reason it is unprofitable to review the literature dealing with enterococcic infections in man other than to point out that these organisms have long been recognized to be occasionally the cause of bacterial endocarditis and to be frequently isolated from infections of the urinary tract. No comprehensive description of the types of disease produced by fecal streptococci is available nor any estimate of the frequency with which they may be recovered from clinical

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1 Andrewes, F. W., and Horder, T. J. A Study of the Streptococci Pathogenic to Man, *Lancet* **2** 708, 775 and 852, 1906

2 Lancefield, R. C. A Serological Differentiation of Human and Other Groups of Streptococci, *J. Exper. Med.* **57** 571, 1933

3 (a) Rantz, L. A., and Keefer, C. S. The Distribution of Hemolytic Streptococci, Groups A, B, and C in Human Infections, *J. Infect. Dis.* **68** 128, 1941. (b) Hare, R. Sources of Haemolytic Streptococcal Infection of Wounds in War and Civil Life, *Lancet* **1** 109, 1940

4 Sherman, J. M. The Enterococci and Related Streptococci, *J. Bact.* **35** 81, 1938

5 (a) Sherman, J. M. The Streptococci, *Bact. Rev.* **1** 1, 1937. (b) Graham, M. C., and Bartley, E. O. Some Observations on the Classification of the Enterococci. *J. Hyg.* **39** 538, 1939

The infectious process was bilateral in 2 instances and unilateral in 4, the same ratio as for group A infections. The onset in both groups almost invariably occurred after an infection of the upper respiratory tract. Treatment was instituted in all 6 cases on the first or second day of illness and consisted of myringotomy and use of the ear washes and nose drops. No sulfonamide compounds were administered. On this regimen 4 patients (66 per cent) recovered completely in an average of twelve days. Fifty-seven per cent of 33 patients with group A infections similarly treated recovered in an average of twenty-five days. Two of the 6 with enterococcic infections of the ear were treated, after twenty-one days of conservative observation, with sulfanilamide, and in the 1 instance in which adequate data are available the disease was immediately arrested. Group A infections similarly treated also responded well, especially if sulfathiazole (2-[paraaminobenzenesulfonamido]-thiazole) or sulfadiazine (2-[paraaminobenzene-sulfonamido]-pyrimidine) was the drug used.

One other instance of enterococcic involvement of the ear has been described in detail elsewhere<sup>11</sup> but may be reviewed at this time.

**CASE 1**—An 18 year old boy had otitis media and mastoiditis, followed by mastoidectomy. At the time of operation an epidural abscess was present but not thrombosis of the lateral sinus. The temperature became elevated postoperatively, and culture of the blood showed nonhemolytic enterococci. Sulfathiazole was administered, and further operative exploration revealed another abscess over the temporal lobes of the brain, which was drained. Cultures of the spinal fluid were sterile. Later several other intracranial abscesses were evacuated, from the contents of each of which enterococci were recovered which were similar to those isolated from the blood. The administration of sulfathiazole was continued, and the patient eventually recovered, after an illness of five months' duration. All of the suppurative areas were subdural, and none penetrated the brain substance.

There can be no question that surgical drainage of these localized collections of purulent material beneath the meninges was necessary for a favorable outcome, and it is impossible to evaluate the role of therapy with a sulfonamide compound in the recovery of this patient. Sulfathiazole was probably not instrumental in controlling the infectious process during the acute phase of the disease when septicemia was present, since improvement followed surgical drainage of purulent collections and was ineffective in the subacute stage.

Enterococci rarely cause pneumonia, sinusitis or pharyngitis, but they occasionally are the etiologic agents in acute suppurative otitis media. This disease, when due to these organisms, usually occurs in infants, in contrast to infections involving streptococci of group A, which are most frequent during early and middle childhood, at the time when other diseases due to hemolytic streptococci are common.

Enterococcic otitis media untreated at the onset by a sulfonamide compound appears to resolve more quickly than do infections caused by members of group A similarly treated. In some cases, however, chemotherapy or surgical intervention is required, and 1 has been described in which the initial infection of the ear was followed by mastoiditis, sepsis and an abscess of the brain. It is believed that sulfathiazole did not definitely affect the course of the infection.

**Cardiovascular System**—Enterococci are important in infections of the cardiovascular system only as etiologic agents in bacterial endocarditis. In a recent review of enterococcic endocarditis, Skinner and Edwards<sup>12</sup> discovered reports of 37 cases of this disease in the literature and added 2 of their own. Description of the etiologic organisms in most of these cases is so meager that it is impossible to determine whether enterococci, according to the criteria of Sherman,<sup>13</sup> were involved.

11 Rantz, L. A. Streptococcal Meningitis, *Ann Int Med* **16** 716, 1942.

12 Skinner, D., and Edwards, J. Enterococcal Endocarditis, *New England J Med* **226** 8, 1942.

as an enterococcus for clinical purposes without recourse to the more elaborate biologic and serologic methods. All of the organisms isolated from human beings, which are described in this report grew at 10 C and 45 C in the presence of 6.5 per cent sodium chloride and 0.1 per cent methylene blue. Half were studied serologically and demonstrated to be members of group D, including nearly all of those from sources other than the urinary tract.

#### SOURCE OF MATERIAL

Enterococci have been isolated from various materials obtained from more than 200 persons during this study. Adequate observations were available in 145 cases from the clinic services of Stanford University Hospitals and have been selected for study. They are presented under several classifications, according to the site of the infection, as is shown in table 1.

*Respiratory Tract*—Extensive studies of the normal flora of the nasopharynx have revealed that hemolytic members of group D are very rarely present.<sup>9</sup> Non-hemolytic varieties are probably also uncommon.<sup>10</sup> No instances of pharyngitis or pneumonia have been observed during the period of observation included in this report in which enterococci could be definitely implicated as etiologic agents. Hemolytic enterococci were isolated as the predominant organisms in 1 case of

TABLE 1—*Distribution of Cases by Site of Infection*

Source	Number of Cases
Respiratory tract infections	8
Cardiovascular infections	3
Abdominal infections	23
Urinary tract infections	105
Miscellaneous infections	6
Total	145

chronic purulent sinusitis of 50 examined. Cultures were positive on four occasions over a period of four months. No specific therapy other than the irrigation of the sinuses was undertaken.

It is evident that enterococci are present at times in the nasopharynx, since in 6 cases they were isolated in pure culture from the pus obtained on the paracentesis knife used to perform a myringotomy for acute purulent otitis media. Five strains were nonhemolytic, and 1 was hemolytic. That these streptococci were the cause of the suppurative process seems definite. During the interval in which these cases were studied, 53 other instances of otitis media caused by streptococci were observed. In every case a member of the Lancefield group A was isolated. Enterococci are therefore responsible for approximately 10 per cent of all streptococcal infections of the middle ear. This fact is of interest and attests the greater invasiveness of these organisms over that of the other nonhemolytic and alpha hemolytic streptococci constantly present in the nasopharynx.

This enterococcal otitis media may well be contrasted clinically with the more frequent type caused by streptococci of group A. All of the patients were infants, the average age being 10 months and the extremes 4 and 15 months. Group A infections were observed in children with an average age of 4.5 years, with extremes of 10 months and 11 years, only 20 per cent being less than 2 years of age.

<sup>9</sup> Rantz, L. A. The Hemolytic Streptococci. Observations on the Carrier State in the San Francisco Area, *J. Infect. Dis.* **69**: 248, 1941. Hare.<sup>3b</sup>

<sup>10</sup> Safford, C. E., Sherman, J. M., and Hodge, H. M. Streptococcus Salivarius, *J. Bact.* **33**: 263, 1937.

CASE 3—A 26 year old man was admitted to the hospital having suffered chills, fever and night sweats for four weeks. He had always been well, and there was no previous history of any illness resembling rheumatic fever or heart disease. He had had a tooth extracted two months before his entry to the hospital, after this he had not been entirely well but was at work until one month later, when he began to suffer from severe night sweats, malaise and loss of weight, followed by the development of chills and fever. At this time he came to the hospital, and his subsequent course is illustrated in the chart.

On examination he was obviously ill and had fever, but no other abnormalities could be discovered except a soft blowing systolic murmur over the precordium. The results of ordinary laboratory procedures were within normal limits, but the first and eleventh subsequent blood cultures revealed nonhemolytic enterococci. Usually about 100 colonies per cubic centimeter were present.

Continuous treatment with sulfathiazole or sulfadiazine associated with pyiotherapy, the latter being administered on sixteen occasions, failed to alter the course of the disease. The spleen became markedly enlarged and tender and the right hip and shoulder acutely painful, and shortness of breath and precordial pain appeared. The final episode was one which simulated the rupture of an intra-abdominal viscus with the development of an acute diffuse peritonitis. The duration of his illness was five and one-half months.

The anatomic diagnosis was subacute endocarditis of the mitral valve (no evidence of previous valvular disease), with (a) septic infarct of the spleen (nonhemolytic streptococci) (b) rupture of the spleen due to infarct, (c) acute peritonitis due to nonhemolytic streptococci, (d) multiple abscesses of the heart, (e) septic infarct of the kidney (no evidence of glomerulonephritis) and (f) septic infarct of the brain.

CASE 4—A 36 year old woman entered the hospital, pregnant and at term, with a complaint of chills and fever for one month. Her course in the hospital is illustrated in the chart. There was no past history of rheumatic fever or heart disease. The pregnancy, her fifth, had proceeded normally until the last month, when chills and fever supervened and continued until her entry into the hospital without localizing signs or symptoms. On examination she was found to be febrile and the signs of free aortic regurgitation were present, but no other abnormalities could be discovered. She was anemic, the hemoglobin content being only 55 per cent (Sahli), the leukocyte count and the urine were normal, and the first and seven later blood cultures yielded nonhemolytic enterococci.

She was delivered of a normal baby on the seventh day in the hospital. Treatment with sulfapyridine followed by sulfathiazole did not alter the outcome but was associated with a brief return of the temperature to normal. Her spleen became palpable and crops of petechiae appeared, but the urine was always normal. She died after an illness of two months' duration.

The important conditions noted at necropsy were subacute endocarditis of the mitral and aortic valves (no evidence of previous valvular disease) with subacute myocarditis and acute focal early suppurative hepatitis.

In the 3 cases of enterococcic subacute endocarditis just presented the clinical course was not unlike that of similar infections due to the more common types of alpha hemolytic and nonhemolytic streptococci usually responsible for this condition. Chills, fever, sweats, heart murmurs, splenomegaly, petechiae and other embolic phenomena were regularly present. In some important respects, however, the disease was different. Severe precordial pain occurred in 2 cases, and repeated examination of the urine failed in every case to demonstrate the signs of nephritis so commonly present in subacute bacterial endocarditis.

At necropsy the observations were distinctive. Suppurative lesions were present in the peripheral organs in every case. In 1 only the liver was involved, in another, the myocardium, spleen, kidney and brain, and in the third, only the spleen. In 1 case rupture of a splenic abscess was followed by acute enterococcic peritonitis with death. The extent of these lesions appeared to be roughly correlated with the duration of the illness. Suppuration such as this occurs in approximately 15 per cent of all cases of streptococcic endocarditis<sup>15</sup> but is very rare in other

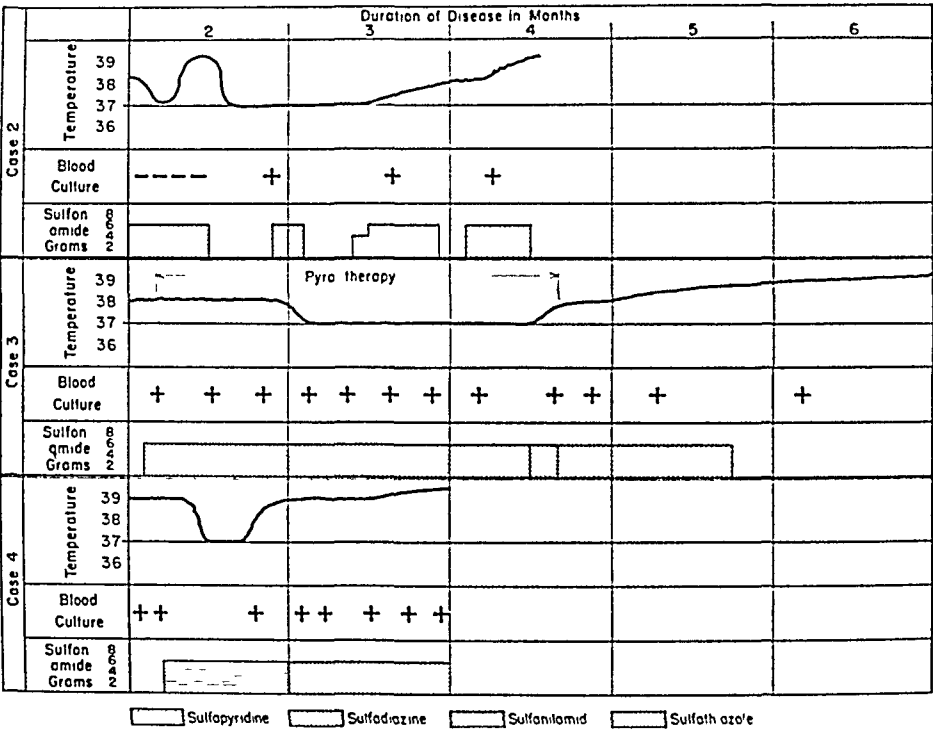
15 (a) Middleton, W. S. *Streptococcus Viridans Endocarditis Lenta*, Am. J. M. Sc. **198** 301, 1939. (b) Thayer, W. S. *Studies on Bacterial (Infective) Endocarditis*, Johns Hopkins Hosp. Rep. **22** 1, 1926.



Twenty per cent of the strains of streptococci recovered in cases of bacterial endocarditis by Moran<sup>13</sup> were enterococci, a value closely approximated during the present study, in which fecal streptococci were isolated in 3 of 16 instances of this disease. These 3 cases will now be described in detail and the clinical and pathologic observations compared with those in 3 published cases<sup>11</sup> in which definite group D enterococci were isolated.

CASE 2—A 33 year old woman entered the hospital with a complaint of chills and fever for three weeks. Her clinical course is illustrated in the accompanying chart. Attacks of pain in the joints with fever had occurred at 14 and 16 years of age, since which time she had been known to have valvular disease of the heart.

The onset of chills and fever three weeks before the patient's entry to the hospital followed a cold and bronchitis which had persisted during the previous month. Immediately after the



Clinical course of 3 patients with enterococcal subacute bacterial endocarditis

first chill severe pain had developed in the left flank, and later she had many red painful swellings of the toes and fingers. No petechiae were discovered on physical examination when she was first seen in the hospital, but there were marked clubbing of the fingers and a palpable spleen associated with the frank signs of mitral stenosis and aortic regurgitation. The urine, red blood cell count and hemoglobin were within normal limits, but the total leukocyte count was elevated to 18,000 per cubic millimeter. Culture of the blood gave negative results until the end of the first month in the hospital, after which nonhemolytic enterococci were recovered on several occasions.

Sulfathiazole appeared to control the fever but caused cutaneous eruptions. The substitution of sulfanilamide and later of sulfadiazine failed to alter the course of the disease, and the patient died, after an illness of three and one-half months, with the development of severe precordial pain, many petechiae and a very large spleen.

The anatomic diagnoses were (1) rheumatic endocarditis of the mitral and aortic valves, (2) subacute endocarditis of the aortic and tricuspid valves with infectious perforation of the interventricular septum, (3) infarct of the spleen, septic (nonhemolytic streptococcal), and (4) infarct of the kidney (no evidence of focal or diffuse glomerulonephritis).

13 Moran, H. Classification of Streptococci from Cases of Endocarditis, *Proc Soc Exper Biol & Med* 38 805, 1938.  
14 Williams, C. Bacterial Endocarditis Due to the Streptococcus Fecalis *Am Heart J* 18 753, 1939. Skinner and Edwards<sup>12</sup>

The pus obtained from 1 patient with an ischioirectal abscess contained many coagulase-positive staphylococci and hemolytic enterococci. Rapid healing occurred after surgical drainage and administration of sulfathiazole. The effect of chemotherapy could not be evaluated. On several occasions enterococci were isolated from operative wounds contaminated with fecal contents. Coliform bacilli were also present.

The nature of the infectious process leading to death in cases of acute peritonitis does not appear to be clearly defined. Observations made during this study are of interest in this respect. Cultures of blood from the heart have been made in 8 instances of abdominal infection following perforation of some part of the gastrointestinal tract. In 3 cases the blood was sterile, *Proteus vulgaris* was recovered in pure culture in 1, and enterococci were isolated in each of the others, twice in association with other organisms. In the 2 last-mentioned cases, culture of the peritoneal exudate revealed the same bacteria as were recovered from the heart's blood.

None of the patients from whom enterococci were obtained lived more than seventy-two hours after the onset of symptoms of peritonitis. No cultures of the blood were made during life, and none of the patients received therapy with a sulfonamide compound.

Enterococci are constantly present in the normal bowel and are therefore frequently recovered in cases of infections of the peritoneal cavity and associated organs, especially when a direct communication with the lumen of the intestine has been established. They are found, usually in association with other organisms, as the etiologic agents in many cases of acute peritonitis. It is of interest that cultures of blood from the heart in 8 instances of this disease revealed enterococci in 4. If it can be shown that the terminal events in fatal peritonitis are frequently associated with a generalized invasion of the body by enterococci, either alone or with other organisms, the rationale of either local or systemic treatment with sulfonamide compounds in such cases becomes less clear, since these organisms are exceedingly resistant to the action of these chemicals.

Antemortem and postmortem cultures of blood and of peritoneal exudate in cases of acute infections of the abdomen are of great importance for the purpose of establishing the nature and extent of the infectious processes in fatal and in nonfatal cases.

*Infections of the Urinary Tract*—A recent study<sup>19</sup> of the urines of 650 patients in the medical wards of this clinic revealed that streptococci could be isolated from 14 per cent of them and that 27 per cent of these organisms were enterococci. A report by Porch<sup>20</sup> also indicates the frequency with which fecal streptococci may be recovered from this source.

A general impression is obtained from previous descriptions<sup>21</sup> of infections of the urinary passages that streptococci are usually responsible for mild disease of these organs, and this view is supported by observations previously made in this clinic.<sup>19</sup> It appeared at that time that the enterococci might cause a more severe infectious process than the other streptococci. The large number of articles<sup>7</sup>

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19 Rantz, L. A. Urinary Tract Infections, in Steele, J. M., and others. *Advances in Internal Medicine*, New York, Interscience Publishers, Inc., 1942, vol. 1, p. 137.

20 Porch, M. L. A Bacteriological Study of Streptococci Isolated from the Urinary Tract, *J. Bact.* **41**: 485, 1941.

21 Culver, H. The Importance of the Streptococcus in Genito-Urinary Diseases, *J. A. M. A.* **103**: 635 (Sept. 1) 1934. Heckel, N. J., Jensen, L. B., and Wood, I. H. Streptococcal Infections of the Genito-Urinary System, *Urol. & Cutan. Rev.* **40**: 564, 1936. Cabot, H. *Modern Urology*, Philadelphia, Lea & Febiger, 1936, p. 513.

than those instances in which enterococci are the cause<sup>16</sup> Furthermore, no evidence of focal or diffuse glomerulonephritis was discovered at necropsy, also an unusual observation<sup>15a</sup>

In 2 of the 3 instances, no underlying congenital or rheumatic abnormalities of the heart valves were discovered Repeated series of observations<sup>15</sup> have shown that in 80 per cent of all cases of subacute bacterial endocarditis some preexisting damage to the endocardium is associated A review of the 3 previously described cases of definite enterococcic endocarditis shows that in 1 the disease was established on a normal valve, in another extensive peripheral suppuration was present, leading to rupture of the spleen and fatal peritonitis, and in a third extensive amyloidosis was discovered In none was a focal or diffuse glomerulonephritis observed

Wallach has previously emphasized<sup>17</sup> the frequency with which suppurative infarction may occur in enterococcic endocarditis and has also described focal myocardial lesions associated with cardiac failure These appear to be no more than a variation of the generalized suppurative process, since in 1 of the cases described in this report frank myocardial abscesses were found

It is possible to say, in summary, that enterococcic endocarditis probably tends to occur in persons with normal heart valves more frequently than do other forms of streptococcic infection of the endocardium Suppuration in the myocardium and in the organs peripheral to the heart occurs uniquely in enterococcic endocarditis and has twice led to splenic rupture and fatal peritonitis Focal and diffuse glomerulonephritis have been conspicuous by their absence

From the standpoint of therapy, sulfonamide compounds and artificial fever have been notable failures In no case was the blood sterilized In 1 instance of tricuspid and aortic involvement, ulceration through the intra-ventricular septum apparently occurred during treatment

*Abdominal Infections*—The presence of enterococci in great numbers in the feces suggests that these organisms should be intimately associated with many infectious processes originating in the peritoneal cavity and its associated organs No direct published evidence is available which is pertinent, since specific differential tests have not been applied to the nonhemolytic streptococci frequently isolated from infections in and about the abdomen It has been pointed out, however that streptococci may be readily isolated from about 25 per cent of the purulent fluids obtained from patients with peritonitis following rupture of the appendix<sup>18</sup>

During the present study enterococci were isolated from several intra-abdominal sources On 5 occasions they were obtained from peritoneal exudates, twice in pure culture Periarthritis nodosa, acute ulcerative enteritis and hemolytic jaundice were the predisposing diseases leading to peritonitis in 3 cases, and in 2 it followed operative rupture of the large bowel or bladder No blood cultures were performed before or after death All but 1 of the patients died The one surviving was treated for seven days with sulfanilamide without its affecting the course of the disease She finally recovered after drainage of an abscess in the cul-de-sac

Nonhemolytic enterococci were isolated in association with colon bacilli (*Escherichia coli*) from the bile of 2 persons with acute cholecystitis and cholangitis Both recovered after surgical intervention, with removal of stones in 1 and release of occlusive adhesions around the common duct in the other The latter patient was twice explored surgically, and the bacterial flora of the bile was similar on the two occasions, one year apart

16 Rantz, L A Unpublished data

17 Wallach, K Subacute Enterococcus Endocarditis, *J Mt Sinai Hosp* 1 80, 1934

18 Altmeier, W A The Bacterial Flora of Acute Perforated Appendicitis with Peritonitis, *Ann Surg* 107 517, 1938

he had taken 12 Gm. The results of physical examination on the patient's entry were not remarkable except for rales at the bases of the lungs and marked enlargement of the prostate. The renal pelvises were lavaged for the purpose of dissolving the probable sulfapyridine calculi, and cultures of urine from this source showed many hemolytic enterococci. After this operation he began to void, but transient enterococcic bacteremia appeared. Many pus cells and organisms were present in the urine at all times. He recovered from the acute attack after a febrile illness of about three weeks without the use of chemotherapy, but the urine was never sterilized.

CASE 6—A 46 year old diabetic woman entered the hospital with acidosis, the carbon dioxide-combining power being 40 volumes per cent. Innumerable white cells were present in the urine on admission, but the temperature was normal. An acute febrile episode supervened on the fifth hospital day, at a time when her acidosis was well controlled. Pain in the flank was absent, but the urine contained many pus cells and 10 million hemolytic enterococci per cubic centimeter.

An indwelling catheter was inserted, and she made an uneventful recovery after a febrile illness of three weeks' duration. Sulfanilamide was administered over a ten day interval in large doses but entirely failed to modify the course of the illness. Since that time she has had repeated episodes of infection of the urinary tract. Coliform bacilli were usually the etiologic agents, but enterococci also were always present.

CASE 7—A 75 year old woman entered the hospital suffering from daily chills and fever for three weeks in association with generalized abdominal pain. Physical examination revealed only moderate tenderness in both lateral aspects of the abdomen and a temperature of 104 F (40 C). The urine contained an immense number of pus cells and nonhemolytic enterococci. The leukocyte count was 22,000 per cubic millimeter.

Her temperature remained elevated for seven days and returned to normal by lysis. Sulfathiazole was administered for seven days after the temperature was normal, and during this time the urine became sterile. She made a complete and uneventful recovery.

CASE 8—A 17 year old girl was delivered of a normal child at term after a prolonged and difficult labor. An eight day febrile episode followed this and was associated with the appearance of huge numbers of pus cells and hemolytic enterococci in the urine. Uneventful recovery occurred and the urine returned to normal without special therapy.

CASE 9—A 59 year old woman whose left ureter was cut during an operation for resection of the rectum had a prolonged febrile postoperative course during which nonhemolytic enterococci and pus cells were present in the urine in large numbers. She eventually recovered but sulfathiazole in adequate dosage failed to influence the course of the disease.

**Factors Predisposing to Infection.** All of the males and two thirds of the females in whom active infectious processes were present showed evidence of obstruction or mechanical manipulation of the urinary passages or suffered from another disease which predisposed to infection of these organs. Prostatic hypertrophy was demonstrated in 10 men, cord bladder in 2, indwelling catheter in 1 and heart failure and diabetes each in 1. Eight of the infections in women followed postoperative catheterization, in 3 the infection was associated with severe cardiac failure, in 2 with renal stone in 2 with diabetes and in 3 with other serious generalized infections.

**Results of Therapy.** Twenty-seven of the group of patients with infections of the urinary tract under discussion received treatment with sulfonamide compounds. For 8 no culture was made before treatment was begun, 13 were found to have a mixed bacterial flora in the urine in association with enterococci, and 6 had the latter organisms present in pure culture. Nearly all of these 27 persons received from 4 to 6 Gm. of sulfathiazole or sulfadiazine a day for seven or more days. A few were treated with sulfanilamide. At the end of the period of chemotherapy enterococci could still be recovered from the urine, usually in immense numbers. In 1 instance the urine was sterile.

Other bacteria which had been present before treatment had, in every case disappeared. It is of the greatest importance to point out that during the progress of chemotherapy in these cases all symptoms of infection of the urinary tract were

describing the extreme resistance of these organisms to sulfonamide compounds in vitro suggests that their eradication from infected urines is an important problem in urologic practice but no adequate description of enterococcal infection of the urinary tract has been discovered.

Members of this group of streptococci have been isolated from the urines of 105 persons during this study. The data on 58 of these will now be considered in detail. The others have been eliminated, since their urines contained less than 500 bacteria per cubic centimeter. It was hoped that a more accurate evaluation of the true importance of the fecal streptococci in infections of the urinary tract might be obtained by eliminating these examples of minimal or questionable infection.

Table 2 presents certain pertinent data in regard to these patients and the organisms isolated from their urines. It will be observed that approximately one third of the diseased persons were males; that the streptococci occurred in pure culture in 58.6 per cent of the cases and mixed with colon bacilli in 22.4 per cent and with staphylococci in 17.3 per cent; and that 27.6 per cent of these persons harbored hemolytic and 13.8 per cent proteolytic enterococci.

Insufficient difference in the type of disease caused by the fecal streptococci in infections of the male and of the female urinary tract exists to justify the description

TABLE 2—*Cultural Observations on Enterococci Isolated from the Urine*

	Males		Females		Total	
	Number	Percentage	Number	Percentage	Number	Percentage
Total number	21	6.1	37	6.9	58	100
Enterococci isolated in pure culture	12	57.2	22	59.5	34	58.6
Staphylococci also present	5	23.8	5	13.5	10	17.3
Coliform bacilli also present	3	14.3	10	28.0	13	22.4
Hemolytic enterococci	8	38.1	8	21.6	16	27.6
Proteolytic enterococci	2	9.5	6	16.2	8	13.8

of the findings in the two sexes separately. The average age of 21 males from whose urines significant numbers of enterococci were isolated was 55, that of females was 39.

**The Infectious Process.** For the purpose of this study infection of the urinary passages was considered to exist only if dysuria, frequency of micturition during the day, pain in the flank or back and fever were present in some combination in association with the presence of abnormal numbers of pus cells in the urine. The application of these criteria to the group of patients under discussion reveals that in 6 males and 12 females, 31 per cent of the total group, no evidence of infection of the urinary tract could be demonstrated. Enterococci were isolated in pure culture from the urines of 17 of these patients.

Eight males and 10 females suffered from typical cystitis without evidence of renal involvement. In the urines of two thirds of these patients other organisms, usually coliform bacilli or staphylococci, were present in the urine in association with the enterococci.

Six males and 15 females presented signs, such as fever and pain in the flank, which indicated the presence of pyelonephritis. In only 5 of the 15 cases were enterococci the sole organisms isolated from the urine. A brief description of these examples of apparently definite invasion of the kidney by fecal streptococci is pertinent.

**CASE 5**—A man of 65 was admitted to the hospital with a history of chills and fever for ten days. Sulfapyridine had been administered elsewhere, and total anuria developed after

## COMMENT

The enterococci form a group of hemolytic and nonhemolytic streptococci of special biologic and serologic properties whose normal habitat is the human bowel. They are exceedingly resistant to the bacteriostatic action of the sulfonamide compounds.

Recent observations have shown that these organisms are more frequently isolated from human clinical sources, other than the respiratory tract, than any variety of streptococci. The study described here was an evaluation of these organisms as a cause of infections in man.

It has been shown that fecal streptococci are infrequently responsible for disease of the respiratory tract, but 7 instances of otitis media have been observed in which these bacteria were etiologically involved. The disease is different from the usual streptococcic infections of the ear in that it occurs in infants and appears to have a shorter and milder course. A peculiar localized subacute meningitis associated with sepsis developed in 1 adult patient.

Enterococci are responsible for approximately 20 per cent of all cases of subacute streptococcic endocarditis. The clinical course of the infection in these cases resembles that caused by the more frequently isolated types of streptococci, but certain differences are apparent. The normal heart is more likely to be affected, and renal lesions are uncommon. Suppuration in the heart muscle and in organs peripheral to the heart probably occurs uniquely in enterococcic endocarditis. The administration of a sulfonamide compound does not sterilize the blood or affect the final outcome in these cases but may cause the temperature to return to normal for a brief period.

Enterococci, usually in association with coliform bacilli, are a common cause of peritonitis and other infections in and about the abdominal cavity. This is especially true if perforation of the gastrointestinal tract has occurred. The presence of fecal streptococci in the heart's blood post mortem in several instances of peritonitis indicates that sepsis due to these organisms may often occur. Their relationship to fatal outcome in cases of acute infections of the abdomen should be further studied.

Culture of the urine frequently reveals that enterococci are present in very large numbers. In many instances no evidence of infection can be discovered. When it is, other organisms are usually associated with the streptococci. Treatment with a sulfonamide compound results in elimination of bacteria other than the enterococci and disappearance of all signs of active disease. These observations demonstrate the very slight inflammatory properties of the enterococci in relation to the urinary passages. Occasionally this group of organisms does cause cystitis or pyelonephritis, and these infections are remarkable principally because of their failure to respond to sulfonamide compounds.

The results of this study indicate that the enterococci are bacteria of relatively low virulence and invasiveness but that they are not infrequently responsible for serious local or generalized infections. Hemolytic enterococci may be readily confused with the important members of group A if methods of identification are not precise. The nature of the infectious process and the response to therapy of disease caused by the two groups of organisms are not the same, so the importance of accurate differentiation between them is obvious.

Further clinical information of importance will probably be obtained as biologic and serologic study of the streptococci is widely applied and more examples of enterococcic infection are discovered and described.

relieved and the urine became free of pus cells in nearly every instance, even though many enterococci could still be isolated

Mandelic acid was administered to 3 of these persons and resulted in a prompt sterilization of the urine in 2

**Comment on Infections of the Urinary Tract** The previously recorded observations indicate that enterococci can be isolated in significant numbers from the urines of certain elderly men and middle-aged women. Very often no evidence of an infection of the urinary tract is demonstrable, and in such cases the enterococci are almost always present in pure culture

In certain instances cystitis or pyelonephritis is present, and in most of these cases other organisms are recovered from the urine in association with the enterococci. In such cases if a sulfonamide compound is given the bacteria other than the streptococci usually disappear, the latter then remain in enormous numbers. In spite of this fact pus cells are absent from the urine and all symptoms have disappeared

All of these observations indicate that the presence of enterococci in the urinary tract does not in most cases produce inflammation, symptoms usually being caused by the presence of associated staphylococci and coliform bacilli

Treatment with a sulfonamide compound practically never causes sterilization of the urine when enterococci are present, but mandelic acid may do so. Since the presence of the streptococci does not always cause definite disease and since the urines of several of the patients already described became sterile spontaneously, there seems to be little indication for the specific therapy of enterococcic bacteriuria in the absence of signs of infection

On a few occasions fecal streptococci were the cause of cystitis and pyelonephritis. In these instances the disease process was similar to that in which other organisms are the etiologic agents. A difference was the failure of some of these patients to respond to treatment with a sulfonamide compound with the usual prompt sterilization of the urine

Mandelic acid should be valuable for the treatment of enterococcic cystitis. Because the limitation of fluids necessary to the administration of this drug is dangerous if pyelonephritis is present, only symptomatic therapy, including the ingestion of large volumes of fluid, should be undertaken in cases in which enterococcic infection of the kidney has occurred

**Miscellaneous Infections**—Nonhemolytic enterococci were isolated in pure culture from material obtained from the interior of the uterus in 2 cases of puerperal fever. One patient had a normal labor, the other, an incomplete abortion. One was treated with sulfanilamide, the other, with sulfathiazole. Both recovered uneventfully after febrile illnesses of three days' duration. Neither appeared to be seriously ill at any time. The etiologic role of the streptococci in these 2 instances of postpartum fever cannot be definitely determined, but it seems probable that they were responsible for the infectious process

Cultures of material obtained from 3 ulcerative lesions of the skin, 1 syphilitic and the others traumatic in origin, revealed nonhemolytic enterococci and staphylococci. The streptococci are to be regarded as probable contaminants of no great significance

Hemolytic enterococci and colon bacilli were recovered from pus aspirated from the right shoulder joint of an elderly man with colon bacillus bacteremia and aplastic anemia. At some time streptococci must have also been present in the blood, but they had disappeared when cultures were first made. He made a good recovery after surgical drainage of the affected joint without chemotherapy

# CONCENTRATION OF CARBON DIOXIDE IN EXPIRED AIR IN HEART DISEASE

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A disturbance in the respiratory function is the outstanding clinical feature of heart disease. Respiration and circulation serve a dual purpose in supplying oxygen to and removing carbon dioxide from the tissues. When the circulation fails respiration is stimulated as a means of compensation. By measuring the extent of this stimulation, the degree of circulatory failure may be estimated. The ordinary methods of measuring respiration are unsatisfactory, the volume of air breathed must be measured in relation to the oxygen absorbed or the carbon dioxide produced. It has been shown that determination of the concentration of carbon dioxide in the expired air is a simple and highly accurate means of measuring respiration<sup>1</sup>. It is remarkably constant in large groups of subjects and shows little variation between the sexes or with wide differences in age.

Dyspnea is a common complaint in hyperthyroidism and in obesity, whether the heart is abnormal or not. Hyperthyroidism and obesity frequently occur in conjunction with heart disease and make the interpretation of dyspnea more difficult.

## THE VOLUME OF RESPIRATION IN HYPERTHYROIDISM

In hyperthyroidism there is a greater demand for breathing. However, if the increase in the volume of respiration is proportionate to the increase in metabolism the concentration of carbon dioxide in the expired air should remain constant. This study is based on 366 consecutively observed patients with hyperthyroidism. As with the group with normal metabolism, patients with known abnormality affecting respiration were excluded. In table 1 the group with hyperthyroidism is compared with the group with normal metabolism.

In hyperthyroidism the concentration of carbon dioxide in the expired air is relatively constant. With progressive elevation of the basal metabolism there is a slight but definite downward trend in the carbon dioxide pressure in both sexes, at its maximum in the very toxic group the difference is only about 3.5 per cent. This downward trend may result from some impairment in the efficiency of the circulation in tachycardia, from a mild acidosis or from the slightly higher average body temperature in hyperthyroidism. However, from the clinical standpoint, it is the striking constancy rather than the small variation which is most impressive. The course of a number of patients with severe hyperthyroidism has been followed through wide ranges of basal metabolism with only small fluctuations in the partial

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1 Boyer, P. K., and Bailey, C. V. Concentration of Carbon Dioxide in Expired Air. Arch. Int. Med. 69: 773 (May) 1942.



## SUMMARY AND CONCLUSIONS

The enterococci form a group of hemolytic and nonhemolytic streptococci of unique biologic properties and are members of the Lancefield group D

Enterococci are exceedingly resistant to the bacteriostatic action of sulfonamide compounds

Enterococci are more frequently isolated from human clinical sources, other than the respiratory tract, than any other streptococci

Enterococci have been demonstrated to cause otitis media, endocarditis and infections of the abdomen and of the urinary tract

The nature and course of these infections have been described

2361 Clay Street

## THE VOLUME OF RESPIRATION IN HEART FAILURE

In patients with cardiac disease dyspnea has been attributed to an increase in ventilation in the presence of a reduction in vital capacity.<sup>2</sup> In 1897 Kraus<sup>3</sup> observed a decrease in the concentration of carbon dioxide in the expired air. Knipping and Moncrieff<sup>4</sup> and McMichael<sup>5</sup> demonstrated that normally ventilation is proportionate to the amount of oxygen consumed and to the amount of carbon dioxide produced and used these ratios as a means of measuring the increased ventilation in heart disease. The hyperpnea of heart disease can be measured accurately by the concentration of carbon dioxide in the expired air under basal conditions.

## THE RELATION OF VENTILATION TO THE DEGREE OF CARDIAC FAILURE

For this study 138 patients with heart disease were examined under basal conditions. Most of these patients had been followed for some time in the cardiac disease clinic, and the diagnosis had been well established by the routine analysis of the history, physical examination and fluoroscopic, roentgenographic and electrocardiographic studies and any other laboratory procedures indicated. Other patients were selected from the hospital wards, where the same procedure was followed in establishing a diagnosis. The patients were classified according to functional capacity, depending on the clinical impression prior to the measurement of the volume of respiration. They were placed in the four classes recommended by the New York and the American Heart Association.<sup>6</sup>

*Functional Classification of Patients with Cardiac Disease*

- Class I Patients with cardiac disease and no limitation of physical activity
- Class II (formerly IIA) Patients with cardiac disease and slight limitation of physical activity
- Class III (formerly IIB) Patients with cardiac disease and marked limitation of physical activity
- Class IV (formerly III) Patients with cardiac disease who are unable to carry on any physical activity without discomfort

No attempt was made to select heart disease of any particular type, and the entire group includes a general cross section of patients with cardiac involvement, the etiologic and functional distribution is shown in table 3. The hypertensive group includes hypertensive patients both with and without demonstrable arteriosclerosis. The arteriosclerotic group all had essentially normal blood pressure.

In table 4 the average ventilation is expressed as the partial pressure of carbon dioxide in the expired air and also as the percentage of hyperventilation above the amount normally expected. A small number of class I cardiac patients had

2 Peabody, F. W., and Wentworth, J. A. Clinical Studies of Respiration. IV The Vital Capacity of the Lungs and Its Relation to Dyspnea, *Arch. Int. Med.* **20** 443 (Sept.) 1917. Peabody, F. W., Wentworth, J. A., and Barker, B. I. Clinical Studies of the Respiration. V The Basal Metabolism and the Minute Volume of the Respiration of Patients with Cardiac Disease, *ibid.* **20** 468 (Sept.) 1917. Harrison, T. R., Turley, F. C., Jones, E., and Calhoun, J. A. Congestive Heart Failure. X The Measurement of Ventilation as a Test of Cardiac Function, *ibid.* **48** 377 (Sept.) 1931.

3 Kraus, cited by Fishberg, A. M. Heart Failure, Philadelphia, Lea & Febiger, 1937.

4 Knipping, H. W., and Moncrieff, A. The Ventilation Equivalent for Oxygen, *Quart. J. Med.* **1** 17, 1932.

5 McMichael, J. Hyperpnea in Heart Failure, *Clin. Sc.* **4** 19, 1939.

6 New York Heart Association, Criteria Committee. Nomenclature and Criteria for Diagnosis of Diseases of the Heart, ed. 4, New York, New York Tuberculosis and Health Association, 1939, pp. 72-73.

pressure of carbon dioxide in the expired air. When hyperventilation does occur in persons with hyperthyroidism, it has essentially the same significance as in persons with normal basal metabolism.

#### THE VOLUME OF RESPIRATION IN OBESITY

For this study a series of 657 women aged 15 to 59 years was selected from the group with normal basal metabolism.<sup>1</sup> The subjects were chosen arbitrarily on the basis of the percentage of the actual weight in excess of the ideal weight calculated from standard height and weight tables. These subjects are grouped in relation to the normal female standard in table 2.

TABLE 1—*The Influence of Hyperthyroidism on the Concentration of Carbon Dioxide in the Expired Air*

Basal Metabolism	Number of Subjects	CO <sub>2</sub> Tension of Expired Air			
		Mean Value, Min. Hg.	Standard Deviation	Coefficient of Variation	Probable Error of Mean
Females					
Normal range	1 613	20.01	1.38	6.9,	±0.002 <sup>a</sup>
+10 to +24	176	19.80	1.29	6.50	±0.006
+25 to +49	88	19.43	1.30	6.70	±0.004
-50 and over	24	19.28	1.31	6.80	±0.18
Males					
Normal range	408	20.1	1.15	7.13	±0.048
-10 to +24	34	19.91	1.64	8.24	±0.19
+25 and over	44	19.61	2.00	10.20	±0.20

TABLE 2—*The Influence of Obesity on the Concentration of Carbon Dioxide in the Expired Air*

	Number of Subjects	CO <sub>2</sub> Tension of Expired Air			
		Mean Value, Mm. Hg.	Standard Deviation	Coefficient of Variation	Probable Error of Mean
All females	1 613	20.01	1.38	6.93	$\pm 0.0023$
Overweight 10 to 19%	193	20.07	1.39	6.94	$\pm 0.067$
Overweight 20 to 39%	257	20.03	1.42	7.10	$\pm 0.060$
Overweight 40 to 59%	122	20.16	1.35	6.70	$\pm 0.08$
Overweight 60 to 79%	46	20.25	1.67	8.25	$\pm 0.166$
Overweight 80 to 183%	34	20.84	1.53	7.35	$\pm 0.177$

The breathing of these obese women so closely paralleled their metabolism that the concentration of carbon dioxide in the expired air remained nearly constant. In the extremely obese subjects, including a number of enormous persons, the partial pressure of carbon dioxide in the expired air was appreciably higher, which indicates a reduction in breathing proportionate to production of carbon dioxide. Through the remaining subgroups there appears to be a very slight tendency to underventilation as obesity progressed. We do not at present have an explanation to offer for this observation. It may be associated with the tendency to elevation of blood pressure in obese subjects. The actual weight of these subjects may in itself have tended to obstruct and depress respiration mechanically. Possibly the tendency to somnolence in obesity was a factor. However, as with variations in sex, age and basal metabolism, the constancy of the partial pressure of carbon dioxide in the expired air is the most striking feature.

about an equal amount for comparable degrees of failure. It is interesting to note that the relation of types of disease within a functional class stands in the same order in all three groups, namely, hypertensive, rheumatic and arteriosclerotic. This sequence may arise from mere chance selection in this relatively small series, its consistency throughout all three classes suggests that it may be significant. It seems reasonable that such qualitative differences should exist between the types of heart disease. In all probability the blood flow through the brain is most effectively maintained with an elevation in systemic blood pressure and least effectively maintained when arteriosclerosis is present without hypertension, rheumatic heart disease falling between the two.

Pain rather than dyspnea is the criterion according to which anginal patients are usually classified. It might be expected that when at rest and without pain these patients would have normal cardiac function. Only a small group of patients

TABLE 6—*Ventilation in the Anginal Syndrome*

	Mean Tension of CO <sub>2</sub> in the Expired Air *	
	Class II	Class III
All patients with cardiac disease	18.55 (61)	15.87 (42)
Patients with angina	18.47 (8)	15.62 (6)

\* Tension in millimeters of mercury, number of subjects in parentheses

TABLE 7—*The Ventilation Response to Digitalization in the Principal Types of Heart Disease and of Rhythm*

Type of Disease	Number of Patients	Mean Tension of CO <sub>2</sub> in the Expired Air		
		Before Digitalis, Mm Hg	After Digitalis, Mm Hg	Percentage of Improvement
Rheumatic	5	13.52	17.23	27.5
Hypertensive	3	14.66	16.82	14.7
Arteriosclerotic	7	14.32	16.27	13.6
Type of Rhythm *				
Regular rhythm	5	13.04	15.33	17.5
Auricular fibrillation	9	11.73	17.29	17.1

\* One patient, in whom conversion to regular rhythm occurred during digitalization, is not included

(14) with the anginal syndrome have been examined in our classified series. In table 6 these have been compared with other patients of the same functional class. It appears that even at rest without pain the anginal patient does not have normal cardiac function. Although these patients complain chiefly of pain, the prominence of this symptom may mask the dyspnea. Probably in all cases of arteriosclerotic heart disease both pain and dyspnea are present in relative degrees.

#### THE RESPONSE OF PATIENTS WITH CARDIAC DISTRESS TO DIGITALIS THERAPY

Fifteen patients with varying degrees of cardiac failure were examined before treatment and one or more times during the course of digitalization. The results are shown in table 7 and in the chart. Ventilation was reduced in all cases. Improvement in the patients with rheumatic heart disease was more striking than in those with hypertension or arteriosclerosis, age is the probable factor. Improvement in patients with a regular rhythm is about the same as in those with auricular fibrillation.

concentrations of carbon dioxide in the expired air within the normal range. Of the 61 class II patients with cardiac disease, only 6 had carbon dioxide tensions at or above 20 mm of mercury, while 17 had concentrations definitely below the range of normal. The average for the entire group shows a significant tendency to hyperventilation. It is interesting that this should be true of patients who are supposed to have only slight restriction in functional capacity. It is all the more impressive since these measurements were made under basal conditions when these patients had no feeling of dyspnea whatsoever. In this series none of the patients in class III or class IV had carbon dioxide pressures within the normal range. From group to group, as the cardiac functional capacity became progressively

TABLE 3—*Distribution of Patients*

Etiologic Classification	Class II	Class III	Class IV
Congenital	2	2	
Hypertensive	11	16	10
Rheumatic		10	11
Arteriosclerotic	15	16	5
Subacute bacterial endocarditis		1	
Syphilitic			1
Hypertensive with renal complications			5
Total	61	45	32

TABLE 4—*Ventilation in Patients with Cardiac Disease Grouped According to Functional Capacity*

	Number of Subjects	CO <sub>2</sub> Tension of Expired Air		
		Mean Value, Mm Hg	Range Mm Hg	Average Hypervent
Normal		20.00	22.50-18.00	
Class II	61	18.55	21.47-16.01	7.8%
Class III	45	15.81	17.56-14.01	26.5%
Class IV	2	13.41	16.06-9.04	48.7%

TABLE 5—*Ventilation According to Etiologic Types in Comparable Degree of Failure*

Type of Heart Disease	Mean Tension of CO <sub>2</sub> in Expired Air *		
	Class II	Class III	Class IV
Hypertensive	19.15 (11)	16.06 (16)	14.26 (10)
Rheumatic	18.51 (5)	15.85 (10)	13.81 (11)
Arteriosclerotic	18.3, (15)	15.61 (16)	13.73 (5)

\* Tension in millimeters of mercury, number of subjects in parentheses

more impaired, the average amount of hyperventilation increased. In severely decompensated cardiac patients this excessive ventilation may be 100 per cent or more above that expected from the rate of carbon dioxide production. To this may be added the additional burden of an increased metabolism resulting from the labored respiration. The greatest degree of hyperventilation has been observed in cases of heart failure with an associated uremic acidosis.

#### THE RELATION OF VENTILATION TO THE ETIOLOGIC TYPE OF HEART DISEASE

In table 5 cardiac patients with comparable degrees of failure, as judged by the functional classification, are grouped according to the principal etiologic types. In general, all three types of heart disease appear to cause hyperventilation of

be interpreted with a knowledge of their variability. When respiration becomes unduly rapid and shallow, inefficiency results not only from a relatively greater proportion of dead space but from an unequal and incomplete expansion of the lungs which tends to interfere with the gaseous exchange.<sup>7</sup>

In table 8 the rate and depth of breathing of the patients with cardiac disease listed in table 3 are compared with those of the 1,745 adult patients in the series with normal basal metabolism. From the cardiac disease group all patients with hyperthyroidism and uremia are excluded, because in both of these conditions the depth of breathing is increased. The average volume of tidal air is larger in males than in females at all ages, the normal value in table 8 is based on the proportion of males to females in each functional class.

As cardiac failure progresses, the increase in ventilation is largely accomplished by an increase in respiratory rate. This is in contradistinction to most other types of increased ventilation in which both the rate and the depth contribute. When compared with that of normal persons the breathing of patients with cardiac disease is not unduly shallow.

TABLE 8—*The Rate and Depth of Breathing in Patients with Cardiac Disease*

	Number of Subjects	Respiratory Rate	Tidal Air Cc per Sq M	Normal Tidal Air, Cc per Sq M
Normal adult subjects	1,745	15.6 ♀ 14.4 ♂	219 ♀ 255 ♂	
Cardiac patients, class II	44	17.2	222	229
Cardiac patients, class III	25	19.5	238	239
Cardiac patients, class IV	20	25.8	221	239

Hyperventilation in a person at rest is observed rarely in routine medical practice, and when it is found the usual cause is circulatory failure. Aside from cardiac disease one must consider the possible presence of acidosis, shock, certain types of severe pulmonary disease, severe anemia, hysteria, and pregnancy.<sup>8</sup>

#### SUMMARY

In man, regardless of age, sex, basal metabolism or state of nutrition, the concentration of carbon dioxide in the expired air is strikingly constant.

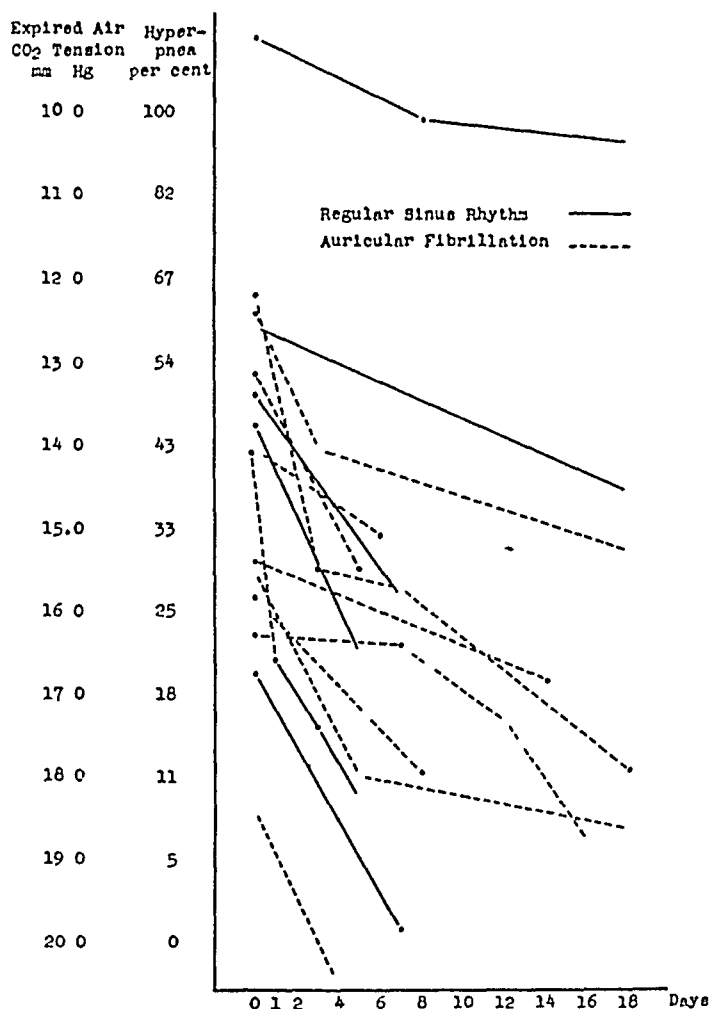
Measurement of the concentration of carbon dioxide in the expired air during the determination of basal metabolism by the open circuit method is a valuable clinical aid in the study of the cardiac status and of the effectiveness of therapeutic measures; it is especially helpful in classifying patients with cardiac disease complicated by hyperthyroidism and obesity. In whom dyspnea on exertion is difficult to interpret, it is unique among methods of estimating cardiac function in that it is performed with the patient at rest; it measures the extent to which respiration compensates for circulatory failure.

7 Haldane, I. S. and Priestley, J. G. *Respiration*. New Haven, Conn., Yale University Press, 1935. Christie, R. V. and Meakins, J. C. *The Intrapleural Pressure in Congestive Heart Failure and Its Clinical Significance*, *J. Clin. Investigation* **13**: 323, 1934.

8 Plass, E. D., and Obst, F. W. *Respiration and Pulmonary Ventilation in Normal Nonpregnant, Pregnant, and Puerperal Women*. *Am. J. Obst. & Gynec.* **35**: 441, 1938.

### THE INFLUENCE OF PAROXYSMAL AURICULAR FIBRILLATION ON VENTILATION

It is generally believed that auricular fibrillation with a rapid ventricular rate is in itself an inefficient rhythm. How much of the inefficiency is due to the rhythm and how much to an underlying organic heart disease is difficult to determine. Patients with hyperthyroidism and without severe organic heart disease are prone to temporary attacks of auricular fibrillation with a subsequent return to normal rhythm and normal cardiac function. In 5 cases of this type normal rhythm was reestablished without the use of digitalis. When the normal sinus mechanism pre-



The respiratory response to digitalization in 15 patients having varying degrees of cardiac failure

ailed, the ventilation was normal, in all cases ventilation was increased during the periods of auricular fibrillation with fast ventricular rate. The average increase in the volume of respiration was 14.4 per cent.

### THE RATE AND DEPTH OF RESPIRATION IN PATIENTS WITH CARDIAC DISEASE

In normal subjects both the respiratory rate and the volume of tidal air are subject to rather wide variation, the coefficient of variation of each is nearly four times that of the partial pressure of carbon dioxide in the expired air. Any statements made about the average respiratory rate and depth of breathing should

## METHODS

Major embolism was produced by the method developed in this laboratory<sup>6</sup> in 24 dogs. Pea or radish seeds were employed to obstruct the moderately sized arteries in 13 dogs, and a 1:20 suspension of starch granules was utilized to induce arteriolar and capillary embolism in 16 dogs. The animals were anesthetized with soluble pentobarbital U S P (sodium pentobarbital) intravenously (25 mg per kilogram of body weight) except in a number of experiments of the major embolism type. In the latter the embolus was passed with the use of local procaine hydrochloride or temporary ether anesthesia. The rate and amplitude of respiration were recorded by a standard pneumograph. In 19 animals (11 with major, 4 with seed and 4 with starch embolism) the respiratory changes were correlated with the changes in pulmonary arterial pressure, which were determined directly from the main pulmonary artery (proximal to the obstruction) by means of the Hamilton needle manometer.<sup>7</sup> In the case of the unanesthetized animals the pulmonary arterial pressure was obtained by use of the London cannula technique developed in this laboratory.<sup>8</sup> The drugs to be used were injected intravenously and 95 per cent oxygen was administered, when desired, by placing the animals in a specially designed oxygen glass chamber and changing its gas content from that of normal atmosphere to as high as 95 volumes per cent of oxygen (O<sub>2</sub>).<sup>9</sup> The oxygen and the carbon dioxide content of the blood were measured from samples of heparinized blood from the carotid artery, withdrawn under oil, prior to and following embolism (and after some of the therapeutic procedures) by the usual Van Slyke method. On several occasions the pH of the serum was determined at the same time by the glass electrode method (Beckman pH meter).<sup>10</sup>

## RESULTS AND THEIR INTERPRETATION

1 *The Changes Observed at Necropsy Following Major Pulmonary Embolism*—In order to interpret the respiratory changes following major embolism, it is essential to appreciate the alterations in the vascular system, heart and lungs demonstrable at necropsy. This interpretation is based on the autopsies of 24 animals with major embolism correlated with notes of the series reported previously from this laboratory.<sup>11</sup>

The effects of the major embolism on the heart were remarkably constant at necropsy regardless of whether the animal succumbed within a few minutes or after several hours. In all, the right side of the heart and the great veins appeared dilated, often to a marked degree. In contrast, the systemic veins were sometimes dilated and engorged and occasionally collapsed, depending on the degree of the pulmonary obstruction and the time of death (cf. previous report<sup>5</sup>). If death occurred early, the lungs appeared slightly emphysematous or more frequently, pale and bloodless. If the animal survived for hours, however, focal areas of pulmonary congestion, edema and atelectasis were frequently discernible. The other viscera presented only varying degrees of passive hyperemia.

2 *The Changes in Respiration Following Major Embolism and Their Cause*—Characteristically, after major embolism respiration quickened (chart 1) and became deepened and markedly labored. All accessory muscles of respiration were brought into action. Usually these alterations gradually became intensified. Terminally respiration usually slowed and appeared gasping and stertorous. The heart usually continued to beat for some time after respiration ceased. At some time during the course of most experiments cyanosis became apparent and was progressively intensified.

These changes in respiration were not dependent on a reduction in the oxygen content of the arterial blood or an increase in its carbon dioxide content in the

7 Hamilton, W. F., Brewer, G., and Brotman, I. *Am J Physiol* **107**: 427, 1934.

8 Katz, L. N., and Steinitz, F. S. *Am J Physiol* **128**: 433, 1940.

9 Dr. D. Cohn, of the department of chemistry, designed this chamber and lent it to us.

10 Dr. I. Kaplan, of the department of chemistry, made these determinations of pH.

11 Megibow, Katz and Steinitz.<sup>5</sup> Mendlowitz.<sup>6</sup>



# KINETICS OF RESPIRATION IN EXPERIMENTAL PULMONARY EMBOLISM

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Previous investigators clearly demonstrated that the invariable response to diffuse embolism of pulmonary arterioles and capillaries is primarily that of tachypnea,<sup>1</sup> while the response following diffuse embolism of the moderately sized pulmonary arteries is characterized by both tachypnea and dyspnea.<sup>2</sup> It was concluded that the underlying mechanism of these respiratory changes was different in that the rapid respiratory rate subsequent to the larger emboli was due apparently to anoxemia while that following the smaller emboli was the result of pulmonary congestion and edema. The latter appeared to operate by reflex action on the respiratory center by stimulation of the vagal nerve endings in the lungs.<sup>3</sup>

During the investigation of the cardiovascular dynamics of and the mechanism of death from experimental pulmonary embolism<sup>4</sup> we had occasion to confirm the essential differences in the character of respiration which follows moderately sized and miliary embolism. During the course of these studies we also noted that obstruction of the main pulmonary artery or of its two major subdivisions is followed by changes in respiration grossly similar to those following moderately sized embolism. The basic factors mediating the respiratory response to such major emboli were not immediately apparent, since arterial anoxemia was not a consistent aftermath<sup>5</sup> and pulmonary congestion and edema, when present, were usually late phenomena.<sup>6</sup>

Experiments were therefore instituted to attempt to elucidate the underlying mechanism of the exaggerated breathing associated with major pulmonary embolism. At the same time, for control purposes experiments patterned after those of Binger, Brow and Branch<sup>3</sup> were performed. Our initial observations when compared with the results of these earlier investigators, however, presented discrepancies sufficient to indicate the need of a more complete reinvestigation of the entire subject. In the course of the present study we also undertook an analysis of the respiratory effects of papaverine hydrochloride atropine theophylline with ethylenediamine, metiazol and paredrine hydrobromide, as well as 95 per cent oxygen, to establish which, if any, of these pharmacologic agents might have therapeutic benefits.

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Aided by the A. D. Nast and the Emil and Fanny Wedeles Fund for Cardiovascular Research

1 (a) Dunn, J. S. *Quart J Med* **13** 129, 1920 (b) Binger, C. A. L., Brow, G. R. and Branch, A. *J Clin Investigation* **1** 155, 1924

2 Binger, C. A. L., Brow, G. R., and Branch, A. *J Clin Investigation* **1** 127, 1924

3 Binger, Brow and Branch (footnotes 1 b and 2)

4 Moore, R. L., and Binger, C. A. L. *J Exper Med* **45** 655, 1927

5 Megibow, R. S., Katz, L. N., and Stemitz, F. S. *Surgery* **11** 19, 1942

6 Mendlowitz, M. *J Thoracic Surg* **8** 204, 1938

In our previous experiments<sup>5</sup> we demonstrated an abrupt elevation in pulmonary arterial pressure above the site of obstruction following major embolism. In eleven experiments of the present series the time relation of the respiratory changes and the changes in pulmonary arterial pressure was analyzed. In five of these experiments the respiratory changes occurred abruptly, almost at once, after the embolization. In these instances it was found that the tachypnea and dyspnea appeared coincidentally with the pulmonary hypertension.

In six of these experiments, however, no changes in rate or depth of respiration were detectable for periods varying from three to eighteen hours after embolism. In these the rise in pulmonary arterial pressure was slight or absent at first and developed only gradually over the next few hours at an accelerating rate, reaching levels of the order found in the experiments with immediate pulmonary hypertension about the time tachypnea and dyspnea developed. Apparently, then, the occurrence of these respiratory changes in major pulmonary embolism is dependent on a certain degree of pulmonary obstruction with a certain level of congestion and hypertension above the site of obstruction and/or a certain diminution in the flow of blood beyond the embolus. In these experiments with delayed effects, apparently the initial obstruction is of insufficient magnitude to lead to respiratory changes. Through the addition of antemortem thrombosis, however (which was demonstrable at necropsy), the obstruction finally reached the critical degree to cause sufficient congestion and hypertension above the obstruction and sufficient interference with flow below it to lead to tachypnea and dyspnea.

By accident it was found that that part of the congestion and hypertension confined to the pulmonary artery above the obstruction and the decrease in flow beyond the pulmonary embolus were not the essential factors. Thus in four experiments the passage of the embolus was followed at once by respiratory changes similar to those found in major pulmonary embolism, and the experiment was judged to be of this sort. Yet at necropsy in these 4 animals the embolus was found to have lodged near the mouth of the superior vena cava. In two other experiments tachypnea and dyspnea were found to occur following the passage of the embolus and the embolus was found at necropsy to have curled up in the right ventricle in such a way as to obstruct flow into this chamber. Experience with 1 dog, in which an embolus was found lodged in the inferior vena cava without obstructing the superior vena cava, demonstrated that interference with flow beyond the obstruction was not the cause of the respiratory changes. The obstruction to flow in this instance seemed as great as in the experiments on pulmonary embolism and embolism of the superior vena cava, and yet during this experiment tachypnea, dyspnea and other significant changes in respiration were absent.

It would appear, therefore, that the common element in the presence of an embolus in the main pulmonary artery or its major tributaries, in the right ventricle or in the superior vena cava at its mouth is congestion in the vascular bed drained by the superior vena cava and its tributaries.

This was tested directly in 3 anesthetized dogs. A metal cannula, 3 mm in diameter, with a small balloon fastened at the end was passed down the right jugular vein to the junction of the superior vena cava and the right auricle under fluoroscopic control. On inflation of the balloon so as to obstruct the flow and stretch this region of the vena cava, an immediate increase in rate, depth and effort of respiration appeared, resembling that noted with major pulmonary embolism. This disappeared when the obstruction was removed by deflating the balloon and the appearance and disappearance of these changes could be caused again and again.

five experiments in which blood gases were measured. Nor were the respiratory changes dependent on the development of an acidemia in the two experiments in which the  $p_{\text{H}}$  of the serum was measured. The development of anoxemia or its aggravation when present at the start of the experiment and the development of hypercapnia and acidemia when they occurred were much later and could have been responsible only in part for the increase in the respiratory difficulty. As a matter of fact with the quickened respiration following the major embolus the arterial oxygen content and oxygen saturation increased slightly, the arterial carbon dioxide content fell slightly and the  $p_{\text{H}}$  of the serum became slightly more alkaline, as might be expected to follow an increase in ventilation. These changes in oxygen and carbon dioxide content can be seen in figure 1 by comparing the first with the second and the fifth set of readings. Apparently, then, the mechanism of the respiratory changes does not reside primarily in the development of anoxemia, hypercapnia or acidemia. This is further indicated, as far as anoxemia is con-

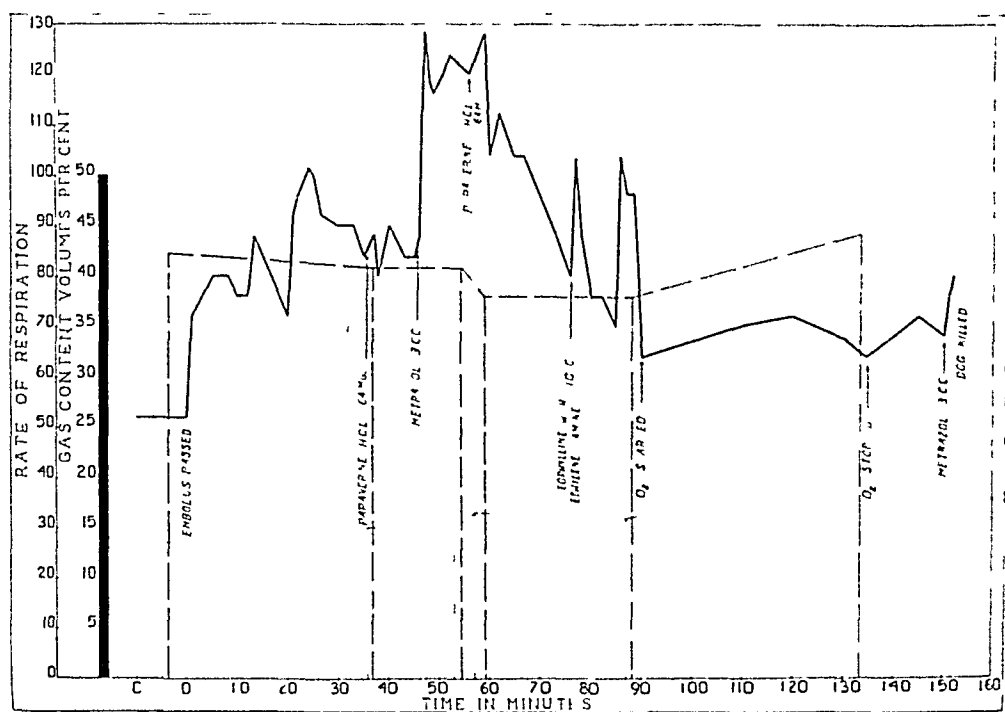


Chart 1—Data obtained in a typical experiment with a major pulmonary embolus. The solid line indicates the rate of respiration, and the dotted line shows the oxygen ( $\text{O}_2$ ) content and the dot-dash line the carbon dioxide content of arterial blood.

cerned, by the experiments with 95 per cent oxygen, in which it was found that while oxygen therapy relieved the cyanosis and arterial anoxemia when present, it had little influence on the respiratory activity (fig. 1).

The fact that pulmonary congestion, edema and atelectasis occur only after a matter of hours as evidenced in our series of autopsies while the respiratory changes come on almost at once after embolization indicates that they too are not the primary mechanism for the tachypnea and dyspnea. This is substantiated by the occurrence of these respiratory changes in animals which succumbed too soon to show pulmonary congestion, edema and atelectasis at necropsy. In time however, if the animal survives, decreases in vital capacity and elasticity of the lungs dependent on pulmonary congestion, edema and atelectasis contribute to augment the already increased respiratory rate and, together with arterial anoxemia, hypercapnia and acidemia, may be in large part responsible for the progression of the respiratory changes in fatal cases.

stimulation in cardiac failure is thus clearly suggested. The dyspnea which occurs with failure of the right side of the heart, therefore, may be, at least in large part, reflex in origin because of distention of the root of the superior vena cava.

*3 The Changes in Respiration Following Diffuse Moderately Sized Pulmonary Embolism and Their Cause*—Seed embolism of the pulmonary arteries which involves moderately sized arteries caused in all 13 animals quickened, deepened and stertorous respiration. While in 7 of the 9 dogs for which such correlations were made cyanosis and arterial anoxemia accompanied these respiratory changes (chart 2, first and second readings), in 2 the respiratory changes definitely preceded the anoxemia and cyanosis. Apparently arterial anoxemia is not necessary to cause the respiratory changes, although it plays a more important role than in the major embolism. In favor of this view is the fact that the inhalation of 95 per cent oxygen by the 2 dogs tested (chart 2), while relieving the arterial anoxemia and cyanosis, caused only a slight or moderate diminution in respiration and did not restore breathing to its preembolic control rate or depth. It is thus apparent that the respiratory changes cannot be explained entirely on the development of arterial anoxemia. This is contrary to the interpretation of Binger, Blouw and Bianchi.<sup>1b</sup>

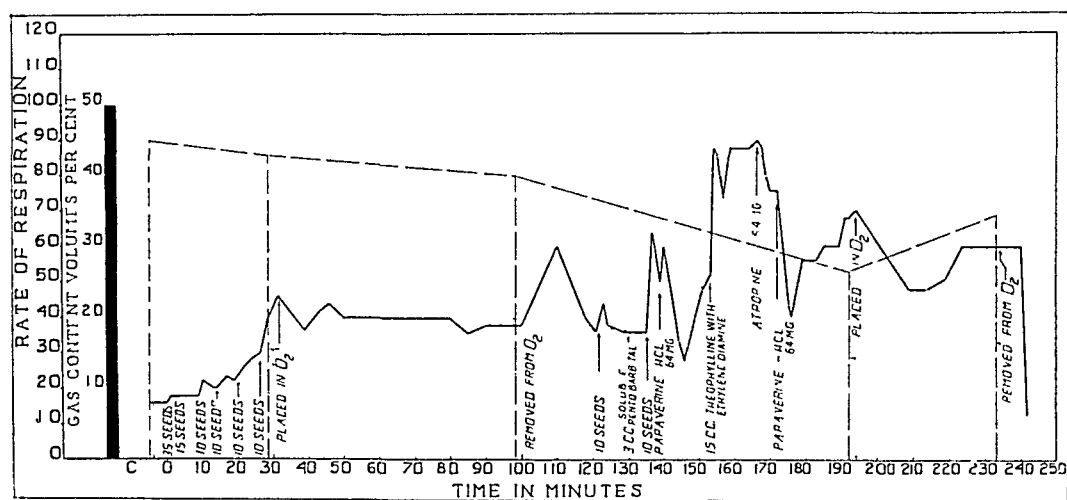


Chart 2—Data obtained in a typical experiment with moderate-sized pulmonary emboli. The solid line indicates the rate of respiration and the dotted line shows the oxygen ( $O_2$ ) content and the dot-dash line the carbon dioxide content of arterial blood.

Similarly, a correlation with the carbon dioxide content of arterial blood in these 9 animals showed no hypercapnia preceding or following soon after the onset of the respiratory augmentation. Thus the carbon dioxide content can be excluded as the etiologic factor. In like manner can pulmonary edema and congestion be excluded as the primary factors, since in 5 animals the characteristic changes in respiration were induced by the injection of large numbers of seeds, which led to a rapid death. At necropsy in such instances pulmonary congestion, edema and atelectasis were absent. Apparently reduction in volume or elasticity of the lungs is not per se responsible for the respiratory alterations, although its presence at necropsy in the animals succumbing after several hours indicates that it plays a later important contributing role.

The onset of the respiratory changes were found to coincide with the elevation in pulmonary arterial pressure in the 4 animals in which these two findings were correlated. Small amounts of seeds failed to cause respiratory changes or pulmonary hypertension. As more seed emboli were injected, greater respiratory changes followed and the pulmonary pressure rose. In the entire series of thirteen experiments a rough proportionality between the number of seeds injected and the mag-

The first possibility that suggested itself was that the respiratory changes were due to stagnation of blood in and slowing of blood flow to the respiratory center, leading directly to alterations in its rhythmic activity. If the tachynea and dyspnea were due to such a central origin, bilateral vagal section should have no effect on the pattern of respiration or, at least, not restore it to the pattern existing before embolization. In four experiments, therefore, bilateral vagotomy was carried out after embolization had led to the characteristic respiratory changes. In all, vagotomy led at once to a restoration of breathing to a rate below the control level; the breathing resembled that observed in animals without emboli following vagotomy. Apparently the central mechanism for the change in respiratory pattern after major pulmonary embolization is excluded, and a reflex origin involving afferent vagal pathways is indicated.

By exclusion, then, the mechanism appears to be reflex in origin; the reflex arising in the congested vessels above the obstruction, namely, in the superior vena cava and its major tributaries. Further, this reflex would appear to be a stretch reflex. Positive evidence in favor of this view was obtained in three experiments in which the umbrella-ribbed cannula constructed in this laboratory for another purpose<sup>12</sup> was used. This cannula it has been shown can distend the vessel at the site of the umbrella ribs when they are extended without obstructing blood flow. Under fluoroscopic control, distention of the junction of the superior vena cava with the right auricle was found in these anesthetized dogs to cause augmentation in the rate, depth and effort of respiration which disappeared when the distention was relieved. These phenomena could be repeated. Apparently by stretch a reflex was set up in this region, presumably in the end organs found by Nonidez,<sup>13</sup> which resemble those of the carotid sinus.

While stimulation of the root of the superior vena cava has been shown to be involved in this reflex stimulation of respiration, the possibility is not excluded that other regions of the superior vena cava and its tributaries, of the right auricle and right ventricle and of the pulmonary artery above the major embolus may also be stimulated by the distention and contribute to the reflex respiratory stimulation. End organs are known to be present in some of these regions, especially at the root of the pulmonary artery.

The interpretation that the changes in respiration in major pulmonary embolism are primarily reflex in origin, set up by stimulation of end organs in the root of the superior vena cava and perhaps elsewhere behind the embolus as a result of distention accounts for all the facts observed in this study. It is, however, likely that subsequently other factors which may develop, such as anoxemia, hypercapnia, acidemia and decreases in the vital capacity and distensibility of the lungs, may contribute to maintain and aggravate the respiratory difficulties. The pulmonary changes may operate by contributing to the changes in gas content and  $p_{\text{H}}$  of the blood or by reflex action arising in the lungs themselves. In much the same way, slowing of blood flow to the respiratory center and stasis in this area may also be contributory, but these are all secondary to the primary reflex stimulation of respiration due to the congestion behind the obstruction, at least in the region of the root of the superior vena cava.

These results with major pulmonary embolism and embolism of the superior vena cava indicate that obstruction and distention not only are significant with embolism but may apply to any variety of distention of the right side of the heart such as occurs in heart failure. The importance of such a reflex origin to respiratory

12 Ballin, I. R., and Katz, L. N. *Am. J. Physiol.* **135**: 202, 1941.

13 Nonidez, J. F. *Am. J. Anat.* **61**: 203, 1937.

imals with other types of embolism, was not restored to the same level by vagotomy, some tachypnea persisted. However, it must be recalled that vagotomy operated in a similar manner in animals with the two other types of embolism in which the congestion was not primarily in the lungs. The possibility, therefore, exists in this form of embolism that congestion of the large pulmonary arteries, the right side of the heart and the superior vena cava may play an important role in causing the respiratory changes. At autopsy, the right side of the heart and large systemic veins in this form as in the other form show marked engorgement. Further, in 5 animals that had characteristic tachypnea postembolically, in which death occurred within two to five minutes following injection of large amounts of starch suspension no evidence of pulmonary congestion or edema was seen grossly or histologically and only minimal histologic atelectasis was present. In these cases some other cause for the respiratory changes than a reflex from the lungs must therefore be sought.

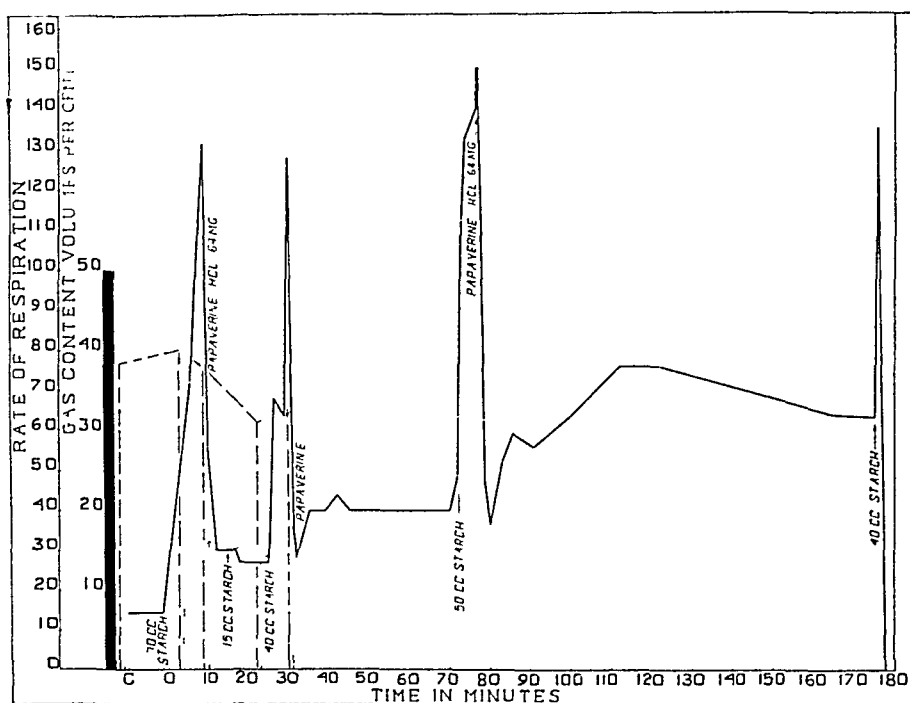


Chart 3—Data obtained in a typical experiment with military pulmonary emboli. The solid line indicates the rate of respiration, and the dotted line shows the oxygen ( $O_2$ ) content and the dot-dash line the carbon dioxide content of arterial blood.

Simultaneous recording of pulmonary arterial pressure and respiration in 4 dogs showed that in this type of embolism as in the others, respiratory changes appeared when pulmonary hypertension occurred. A certain minimal amount of starch suspension was required to cause both. Once tachypnea developed, it persisted and became intensified, and at the same time the pulmonary arterial pressure rose. The tachypnea here is thus again related to the obstruction, with its associated congestion behind the obstruction. It does not appear to be due to local irritation by the starch granules acting as foreign bodies, since if this were the case no aggravation of tachypnea with time should occur. This progression with time and the associated rise in pulmonary pressure appear to be due to the development of ante-mortem clots around the starch granules demonstrable at post-mortem examination.

There is therefore no reason to doubt that a reflex mechanism exists with this form of embolism similar in nature to that associated with the major and

itude of the respiratory changes could be established. The constancy of this correlation between pulmonary hypertension and respiratory stimulation suggests that in this form of embolism, as in major embolism the mechanism for the respiratory changes resides in the vascular congestion behind the embolic obstruction. Thus, as in the major embolism, the mode of production of the respiratory alterations is presumably reflex in origin. In favor of this view is the fact that in two experiments section of both vagus nerves led to a marked slowing of respiration and the assumption of characteristic breathing seen in animals without embolization following bilateral vagotomy.

The possibility exists that in this form of embolism the respiratory changes are set up by irritation of end organs located in the pulmonary vessels by the seeds themselves acting as foreign body irritants. Against this view is the fact that the changes in breathing once established tend to intensify progressively even though no further seeds are injected. This appears to be due to further obstruction of the pulmonary vessels by ante-mortem clot shown at necropsy to develop around the seeds and suggested by the gradual progressive rise in pulmonary arterial pressure.

All the findings in seed embolism of the pulmonary arteries therefore, point to reflex respiratory stimulation which is consequent to distention of the vascular bed behind the embolic obstruction and is of a nature similar to that observed in major pulmonary embolism. A certain degree of distention is essential before this respiratory reflex is established, and its magnitude appears roughly proportional to the extent of the distention. This is not surprising in reflex action with a threshold in which more and more units are brought into play or the rate of discharge of those already operating can be increased.

In this form of embolism however arterial anoxemia and pulmonary congestion and edema play more significant subsidiary roles in the later stages in contributing to the respiratory changes than in major pulmonary embolism.

4 *The Changes in Respiration Following Diffuse Pulmonary Arteriolar and Capillary Embolism and Their Cause*—Unlike major and moderate-sized embolism, diffuse minor embolism produced by starch resulted in tachypnea unaccompanied by hyperpnea or dyspnea in our sixteen animal experiments. Like Binger and his associates<sup>11</sup> we were unable to find any consistent correlation between the tachypnea and arterial anoxemia or hypercapnia. We made no correlation with  $p_{H_2}$  of the blood but they reported also that no correlation could be made between the tachypnea and the  $p_{H_2}$ . In our series, however, arterial anoxemia developed early (chart 3, first and second samples, third and fourth samples) and seemed to play a significant part in the tachypnea. It is well known that shallow rapid breathing may be ineffective in ventilating the lungs, and regardless of its cause, can by itself lead to anoxemia and hypercapnia, so that these changes may be the result of the tachypnea, the anoxemia tending to perpetuate the tachypnea. In 2 of these animals administration of 95 per cent oxygen relieved the anoxemia and cyanosis but had only a slight effect on respiration. Binger, Brown and Branch<sup>12</sup> concluded from their studies that the tachypnea was the result of a reflex from the lungs carried to the respiratory center via the vagus nerves following the pulmonary congestion and edema which these emboli produce. The importance of this factor is supported by our experience, since pulmonary changes occurring after the starch embolization could be demonstrated much earlier than with the moderate-sized (seed) emboli, as our necropsy studies showed. The ability to slow the rate of breathing in 2 animals by bilateral vagotomy favors the view of a reflex mechanism of such pulmonary congestion but does not exclude the important mechanism of its causing anoxemia. Since the breathing in these animals, unlike that in the ani-

was decreased and made less difficult with moderate-sized and to an occasional minimal extent with major pulmonary embolism. The preliminary stimulation of respiration lasted ten to fifteen seconds, was at times pronounced and was similar to the effects of papaverine observed in anesthetized dogs without embolism. It is due to a direct stimulation of the respiratory center by the benzylisoquinoline alkaloids contained in this drug. The slowing and deepening of respiration which followed this preliminary effect appeared peculiar to the type of pulmonary embolism produced by minute emboli, with which there was a long-lasting effect, two to ten minutes or more (chart 3), during which the pattern of respiration was restored almost to normal. This effect could be maintained by administration of another dose of the drug when the effect of the preceding injection was dissipated. With moderate-sized pulmonary embolism this slowing effect was less marked, shorter in duration and associated with lessening of effort and depth of breathing. With major pulmonary embolism the slowing was still less pronounced and frequently entirely absent. When it occurred with major embolism, the depth and effort of respiration were lessened.

There can therefore be no doubt that papaverine exerts a useful role in restoring the kinetics of breathing to normal after pulmonary embolism, especially with the minute variety. It thus has a direct beneficial action in cases of pulmonary embolism aside from its action in dilating the coronary vessels<sup>15</sup> and preventing the occurrence of ectopic ventricular beats, which might cause death by leading to ventricular fibrillation.<sup>16</sup>

Some evidence suggesting that papaverine operates directly on the pulmonary vascular bed was obtained in the following observations. In the 4 experiments with minute pulmonary embolism in which pulmonary arterial pressure was recorded simultaneously with respiration it was found that this drug caused at the time of respiratory slowing a decrease in pulmonary diastolic pressure despite the rise in systolic pressure, indicating a lessened resistance in the pulmonary bed. Visualization of the right ventricle, pulmonary conus and pulmonary bed in 2 other experiments on dogs with minute pulmonary embolism by means of injection of 70 per cent diodast and roentgen examination showed a decrease in the size of the right side of the heart and pulmonary bed following the use of papaverine hydrochloride. These two types of observations suggest that this drug operates to reduce the resistance of the pulmonary arterial bed in pulmonary embolism, thereby relieving the congestion behind the obstruction and lessening the primary and subsidiary factors responsible for altered breathing. If this action were to dilate further the unobstructed peripheral pulmonary channels, especially if these are constricted—as assumed by many—it is apparent that its effect would be greater in peripheral types of embolism than in more central ones. For example Landowne<sup>17</sup> in this department has demonstrated that when central arterial occlusion is present in the limb of man peripheral dilator procedures are less effective than normal in increasing flow.

These experiments with papaverine also support the view derived from other experiments presented in this report that the tachypnea occurring after minute embolization is primarily due to a reflex caused by distention of pulmonary arteries above the obstruction. Some support is lent also to the reflex origin of the respiratory changes in moderate-sized and major embolism.

15 Lindner, E, and Katz, L. N. *J Pharmacol & Exper Therap* **72** 306, 1941.

16 Lindner, E, and Katz, L. N. *Am J Physiol* **133** 155, 1941. Elek, S., and Katz, L. N. *J Pharmacol & Exper Therap* **74** 335, 1942.

17 Landowne, M. *Am Heart J* **24** 50, 1942.



moderate-sized pulmonary embolism. But with this variety, unlike the others it is moderated by some other mechanism. In part, the other mechanism is due to the anoxemia which develops early, and in part it may be a reflex from the congested lungs, as suggested by Binger, Biow and Branch.<sup>10</sup> Neither of these two mechanisms, however, appears to explain all the findings. We therefore suggest the possibility that a reflex originates not in the lungs or the superior vena cava but in the smaller pulmonary arterial branches distended by the obstruction caused by the starch granules. This leads to the peculiar tachypneic respiration and overpowers the reflex arising in the superior vena cava and perhaps in the root of the pulmonary artery, which causes hyperpnea and dyspnea in other types of pulmonary embolism. These distended arteries may be so located as not to alter appreciably vital capacity or elasticity of the lungs, and in that sense our hypothesis differs from that of Binger, Biow and Branch.

Our results suggest, therefore, that end organs located in the vascular tree, in the root of the superior vena cava and probably elsewhere, as in the root of the pulmonary artery and the smaller pulmonary arteries, are susceptible to stretch, which initiates alterations in breathing patterns, the pattern of breathing produced is dependent on the site of the end organs so stimulated.

*5 The Therapeutics of Rapid Breathing in Experimental Pulmonary Embolism*—In a discussion of the therapeutics of pulmonary embolism, obviously the beneficial and deleterious effect of various drugs and procedures on all aspects of pulmonary embolism should be considered. For example, it is apparent that oxygen therapy is indicated whenever arterial anoxemia occurs, in order to obviate the deleterious effects of lack of oxygen. In this report, however, we shall confine ourselves solely to the possible demonstrable effects on the respiratory alterations.

It has already been noted in the preceding sections of this report that oxygen therapy, while relieving anoxemia when present with pulmonary embolism, was not equally effective in altering respiration with the different varieties of pulmonary embolism. Its effects were least with major pulmonary embolism and greatest with minute embolism, in the presence of moderately sized embolism its effect on breathing was intermediate between the first and the second type. It appears that oxygen therapy has its greatest benefit on respiratory effort in overcoming the rapid shallow type of breathing, this is important since it lessens the tendency for ineffective ventilation, which is part of this type of respiration.

Of the drugs tested only papaverine had a consistent and possible beneficial influence. Paredrine hydrobromide solution<sup>11</sup> (2 cc), used 5 times, caused an increase in rate, depth and effort of breathing in animals with all types of pulmonary embolism and hence would exert a detrimental influence on respiration. Atropine sulfate ( $\frac{1}{2}$  grain [0.03 Gm]), used 13 times, theophylline with ethylenediamine (10 to 20 cc), used 14 times, and metrazol (3 cc of 10 per cent solution), used 6 times, exert a variable effect (charts 1 and 2). The inconstancy of the results with these drugs, which were not dependent on dosage or type of embolism make them unreliable for relieving the dyskinetics of respiration.

Papaverine hydrochloride, 32 to 64 mg given intravenously, was used 9 times with major, 7 times with moderate-sized and 15 times with minute pulmonary embolism. In all instances it caused a diminution in rate of respiration after a variable preliminary acceleration. This was most marked in the animals with minute and moderate-sized pulmonary embolism and least marked in those with major embolism. The depth of breathing was increased with minute embolism and

14 Paredrine hydrobromide is p-hydroxy- $\alpha$ -methylphenylethylamine hydrobromide. It was used in an aqueous solution containing 20 mg per cubic centimeter.

# ELECTROCARDIOGRAPHIC CHANGES WITH EXERCISE

## THEIR RELATION TO AGE AND OTHER FACTORS

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The sensitiveness of the electrocardiograph to various stimuli and the consequent variation in tracings taken from the same person make it an important instrument in the study of myocardial function. Important also is the determination of normal variations under the stress of these stimuli.

Changes in the ventricular complexes during attacks of angina have long been recognized.<sup>1</sup> Similarly well known is the demonstration in latent coronary disease of characteristic electrocardiographic deviation after exercise. But<sup>2</sup> it has been pointed out also that inversion of the T wave may occur with such functional disorders as neurocirculatory asthenia and thyrotoxicosis.<sup>3</sup> It has been shown that excessive tobacco smoking can produce depression or inversion of the T wave.<sup>4</sup> Alkalosis and acidosis, the former produced by the simple procedure of hyperventilation with deep breathing, affect the amplitude of the T wave.<sup>5</sup> Anoxemia may flatten the T wave and depress the ST segment in normal persons.<sup>6</sup> Fear will produce changes in the T wave and ST segment similar to those of coronary disease,<sup>7</sup> and the mere taking of food may have its electrocardiographic response.<sup>8</sup>

A study by Tuttle and Korns<sup>9</sup> of electrocardiograms of 48 young male athletes taken before and after a season of training and competition showed changes in only 4 of the subjects. These changes mainly involved the T wave in lead III. One man had a diphasic T wave in lead II on the second tracing. Butterworth

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1 (a) Missal, M. E. Exercise Tests and the Electrocardiograph in the Study of Angina Pectoris, *Ann Int Med* **11** 2018 (May) 1938. (b) Katz, L. N., and Landt, H. Effect of Standardized Exercises on the Four-Lead Electrocardiogram, *Am J M Sc* **189** 346 (March) 1935. (c) Vela, M. Electrocardiographic Observations on Four Cases of Angina Pectoris During Attacks, *Arch cardiol y hemat* **16** 1 (Jan) 1935.

2 Duchosal, P. W., and Henny, G. Modifications of the Electrocardiogram After the Exertion Test. Their Interest in Disorders of the Coronary Circulation, *Helvet med acta* **3** 652 (Oct) 1936. Missal<sup>1a</sup>. Katz and Landt<sup>1b</sup>.

3 Graybiel, A., and White, P. D. Inversion of the T Wave in Leads I or II of the Electrocardiogram in Young Individuals with Neurocirculatory Asthenia, with Thyrotoxicosis, in Relation to Certain Infections, and Following Paroxysmal Ventricular Tachycardia. *Am Heart J* **10** 345 (Feb) 1935.

4 Graybiel, A., Starr, R. S., and White, P. D. Electrocardiographic Changes Following the Inhalation of Tobacco Smoke, *Am Heart J* **15** 89 (Jan) 1938.

5 Barker, P. S., Shrader, E. L., and Ronzoni, E. Effects of Alkalosis and Acidosis upon the Human Electrocardiogram, *Am Heart J* **17** 169 (Feb) 1939.

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7 Mainzer, F., and Krause, M. Changes of Electrocardiogram Brought About by Fear. *Cardiologia* **3** 286, 1939.

8 Gardberg, M., and Olsen, J. Electrocardiographic Changes Induced by the Taking of Food, *Am Heart J* **17** 725 (June) 1939.

9 Tuttle, W. W., and Korns, H. M. Electrocardiograph Observations on Athletes Before and After a Season of Physical Training, *Am Heart J* **21** 104 (Jan) 1941.

## CONCLUSIONS

1 Respiration following embolism of major and moderately sized pulmonary arteries is characterized by tachypnea, dyspnea and hyperpnea, that following embolism of pulmonary arterioles and capillaries is characterized primarily by tachypnea

2 These changes are not dependent on anoxemia since the onset of rapid breathing is not infrequently associated with an increase in the oxygen content and per cent oxygen saturation of the arterial blood

3 Alterations in carbon dioxide content and in  $p_{\text{H}}$  of the blood similarly play insignificant roles, since hypercapnia is inconstant and when occurring is transitory, while respiratory variations occur prior to any tendency to acidemia

4 Actual decreases in volume and variations in elasticity in the lungs, such as follow congestion, edema and atelectasis, while later adding definitive increases to the already accelerated respiration are by themselves not fundamentally implicated

5 Evidence is presented to show that the respiratory changes are not mediated centrally by circulatory slowing through the respiratory center

6 The fact that bilateral vagotomy constantly converts rapid postembolic breathing into slow vagal breathing is utilized as further evidence that the production of rapid breathing is peripheral rather than central

7 The intimate relation of vascular obstruction to rapid breathing is indicated, and the fundamental mechanism with all varieties of pulmonary embolism is shown to be stimulation by distention of afferent nerve endings scattered throughout the pulmonary arterial bed right side of the heart and superior vena cava

8 Through rapid increases in elasticity of the lungs secondary reflexes are initiated, altering the primary respiratory response, and these account for the absence of dyspnea and hyperpnea in military embolism

9 A brief consideration of the therapeutics of postembolic respiration shows that of the drugs studied only papaverine exerts any beneficial action

10 There is a possibility that reflexes of similar origin may be responsible for dyspnea in congestive heart failure and acute failure of the left side of the heart

average score was made by the nonsmokers under 40 and the lowest by the smokers over 40. In fact, the use of tobacco was obviously almost as potent a factor in lowering the index as was age. In the group as a whole the ratio of those with an index above average to those with an index below average was 2 to 1.

#### THE ELECTROCARDIOGRAM BEFORE EXERCISE

In a study of the electrocardiograms of the aged (made with a group of supposedly healthy persons over 70 years of age) Levitt<sup>11</sup> found an increase in the QRS and PR intervals and concluded that this might be considered a normal finding in old age. As shown in table 3, our over-40 group had actually slightly shorter auriculoventricular and intra-ventricular conduction times than did the under-40 group.

TABLE 2—*Schneider Index Averages as Affected by Age and Smoking*

Group	Number of Subjects	Average Index
Whole series	100	14.85
Subjects under 40	50	15.6
Subjects over 40	50	14.1
Smokers under 40	29	15.2
Nonsmokers under 40	21	16.2
Smokers over 40	29	14.0
Nonsmokers over 40	21	14.3

\* Possible maximum score, 18

TABLE 3—*Conduction Time Averages as Affected by Age and Exercise*

	Under 40	Over 40
Before exercise	(50 subjects)	(50 subjects)
PR <sub>2</sub>	0.174	0.172
QRS <sub>2</sub>	0.061	0.056
After exercise	(3 subjects)	(6 subjects)
PR <sub>2</sub>	—0.02	—0.03
QRS <sub>2</sub>	±0.02	±0.03

#### THE ELECTROCARDIOGRAM AFTER EXERCISE

Changes in conduction time with exercise were rare and insignificant and were found in both age groups. When such changes did occur, the PR interval in lead II was decreased, and the QRS interval in that lead was sometimes increased and sometimes decreased, but by such small amounts as to leave the intervals still well within normal limits.

Perhaps the most interesting and unexpected change after exercise was the alteration of the P wave in lead CF<sub>1</sub>. This alteration was in most instances a frank inversion, and similar inversion was found only once in any other lead. It occurred in the electrocardiograms of 44 per cent of the whole group and, as shown in table 4, about twice as often in those of subjects under 40 as in those of men over 40. It occurred also more frequently in the electrocardiograms of smokers than in those of nonsmokers. Physical fitness as measured by the Schneider index was not a factor, however, since the change was shown as frequently by the over-average as by the under-average group. The possible significance of these figures is intriguingly uncertain.

and Poindexter,<sup>10</sup> interested chiefly in the question of the possible effect on the heart of blows on the chest, took electrocardiographic tracings of 35 boys and young men (aged from 16 to 24) before and immediately after boxing matches. They tabulated in detail minor changes in all the complexes, but in their conclusion they mentioned as worthy of note only the increase after exercise of the amplitude of the P wave in leads II and III and a decrease in the size of the T wave.

In our investigation we studied the immediate electrocardiographic response of normal persons to vigorous participation in various sports and correlated these findings with the factors of age, smoking and cardiovascular stability as measured by the Schneider index. As stated before, it would seem that tabulation of normal variations both in the resting state and after exercise might be of particular value.

METHOD OF STUDY

We picked at random 100 men from various groups that met regularly for exercise and recreation. The occupational and social status of the groups was diversified. The youngest subject was a 21 year old swimmer and the oldest a 67 year old volleyball player. For the purpose of statistical study the series was divided equally into those under 40 years and those over 40 years of age. The average age of the under-40 group was 30.7 years, as compared with 49.1 years for the over-40 group—a difference of nearly 20 years. Sports or activities participated in by the men examined were handball, squash racquets, volleyball,

TABLE 1—Averages of Subjects Studied, with Respect to Age, Smoking and Schneider Index

Average age of subjects under 40	30.7 yr
Average age of subjects over 40	49.1 yr
Smokers	58%
Nonsmokers *	42%
Schneider Index	
Over average *	66%
Under average *	34%

\* The average Schneider Index of the whole group was 14.85

badminton, tennis, swimming, rowing, medicine ball, gymnasium apparatus work, bag punching and rope skipping, with the usual one-half to two hour workout. The study in each case was as follows. The subject was seen immediately before he exercised and was questioned briefly in regard to known physical defects. Any one with cardiovascular disease was eliminated. Each subject was then given a Schneider index rating, which is obtained by a test of cardiovascular function and stability based on the reaction of blood pressure and pulse rate to change of position and exercise. This test will not reveal any organic cardiovascular disease unless there is secondary myocardial insufficiency, but it gives a fairly accurate indication of neurovascular fitness. The maximum score is 18, and any figure under 9 may be considered to be indicative of intrinsic myocardial damage. The next step in the examination was making an electrocardiogram with the subject in a recumbent position. He then took his exercise and returned immediately afterward for a second electrocardiogram. Because we wished to know what effect, if any, smoking might have on the Schneider index and on the electrocardiographic changes, notation was made as to whether the subject was a smoker or a nonsmoker. It is of interest that there was exactly the same percentage of smokers in both age groups, namely 58 per cent (table 1).

THE SCHNEIDER INDEX

Before we proceed with a discussion of the electrocardiographic findings a resume of the Schneider index ratings makes an interesting corollary. As indicated in table 2, the average for the whole group was 14.85. In our tabulations, therefore, 15 was considered as above average and 14 as below. The difference of 1.5 between the two age groups, though definite, is inconsequential. The highest

10 Butterworth, J. S., and Poindexter, C. A. An Electrocardiographic Study of the Effects of Boxing, *Am Heart J* 23:59 (Jan) 1942.

lead  $CF_4$  which becomes upright after exercise, and another flattened and distorted T wave in that lead which assumes a normal configuration after exercise. Both these tracings are from handball players in their early thirties who had maximum Schneider index ratings (18) and who were obviously free from any



Fig 1—Lead IV Changes in T wave A, negative T wave becomes upright after exercise and P wave is inverted B, change in contour of T wave after exercise, also inversion of P wave after exercise



Fig 2—Lead III Changes in T wave A, negative T wave becomes positive after exercise B, negative T wave becomes diphasic after exercise and QRS excursion becomes variable

cardiovascular disease. In figure 2 are two examples of change of T from negative to positive, or diphasic deflection. A  $T_1$  which changes from positive to diphasic is to be seen in figure 4 and in our series was a similar conversion of

The susceptibility of the T wave to various stimuli has already been mentioned, and a study was therefore made of this phenomenon in the various groups. It occurred most frequently in leads III and CF<sub>1</sub> and consisted normally of changes in voltage, equally divided between increases and decreases. As shown in table 5, these changes in the T wave after exercise were found in 65 per cent of the whole group and more frequently in the under-40 than in the over-40 group. As with changes in the P wave in lead CF<sub>1</sub>, the Schneider index was

TABLE 4—Changes in P Wave in Lead CF<sub>1</sub> After Exercise in Relation to Age, Smoking and Schneider Index

Incidence 44 per cent of whole group			
Group	Number in Group	Number of Subjects with Change in P <sub>1</sub>	Per Cent of Group
Under 40	30	29	78
Over 40	30	15	30
Smokers	38	29	60
Nonsmokers	42	15	26
Index over average	66	20	45
Index under average	34	14	41

TABLE 5—Change in Voltage of T Wave After Exercise in Relation to Age and Smoking

Incidence 63 per cent of whole series			
Group	Number in Group	Number of Subjects with Change in T	Per Cent of Group
Under 40	50	6	72
Over 40	50	29	78
Smokers	38	44	76
Nonsmokers	42	21	50
Index over average	66	42	64
Index under average	34	23	68

TABLE 6—Change in Voltage of QRS Complex After Exercise \*

Incidence		Percentage of Group	
Under 40		78	
Over 40		84	
Voltage	Instances	Millivolts	
Increased	60	+0.3	
Decreased	40	-0.4	

\* Changes in QRS occur in all leads but are greatest and most frequent in lead IV, and age is not a factor.

not a factor, but alterations in the T wave were found more frequently in smokers than in nonsmokers. A change in the QRS excursion after exercise was the most common phenomenon of all. It was found in 81 per cent of all subjects and with the same frequency in both age groups. Increases were more frequent than decreases (3 to 2). The degree of change varied from 0.1 to 1.0 millivolt, the average increase being 0.3 millivolt and the average decrease 0.4 millivolt. Changes were most common and of greater degree in lead CF<sub>1</sub>. These figures are recorded in table 6. In the course of the study a few electrocardiographic curiosities were discovered which are worth reporting. In figure 1 is seen an inverted T wave in

Schneider index of 18. These abnormalities which might raise some suspicion as to the integrity of the myocardium were found almost entirely in the under-40 group, in young adults with high Schneider index ratings

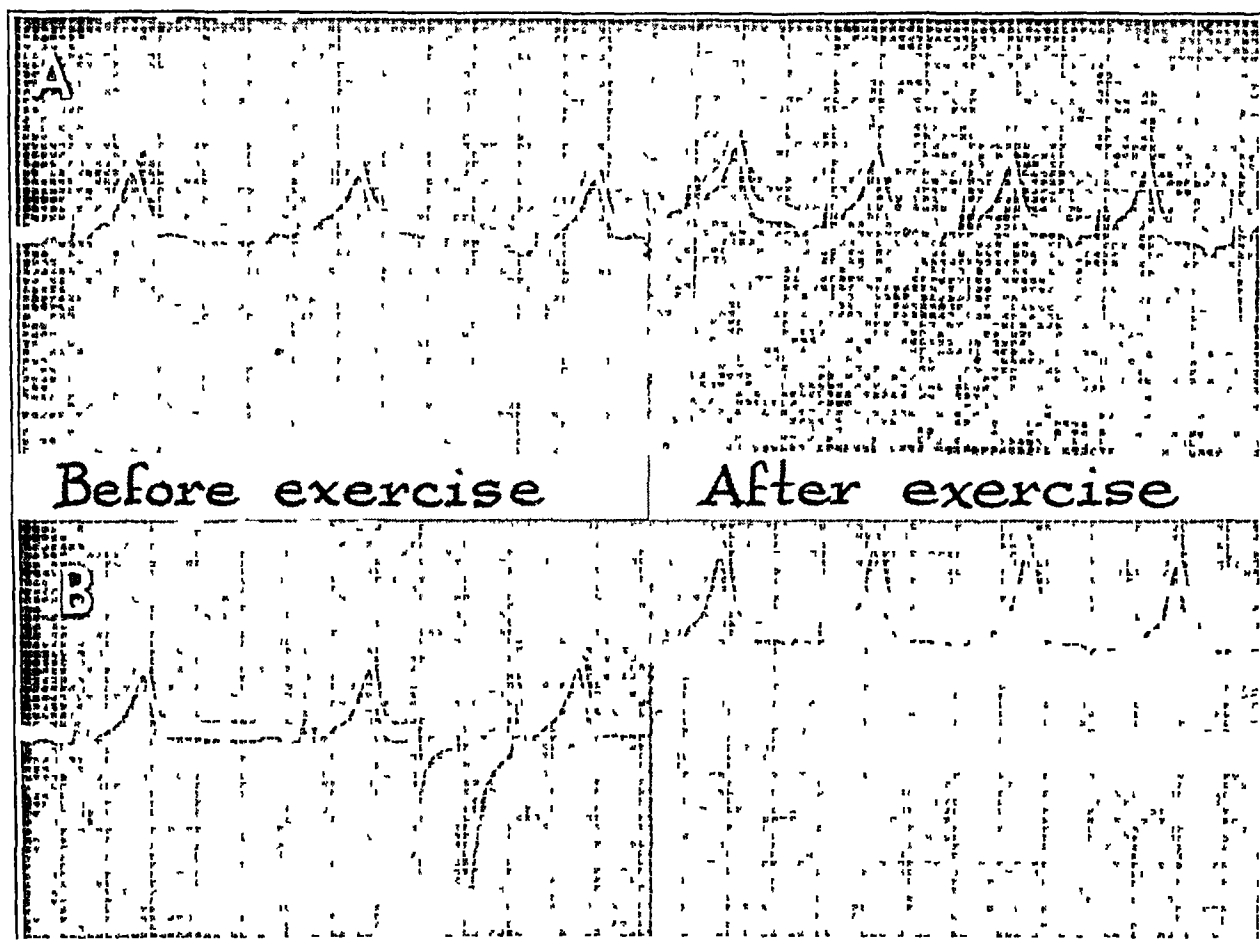


Fig 5—Lead IV. Changes in P wave and QRS complex. *A*, inversion of P wave and splintering of QRS complex after exercise. *B*, inversion of P wave and disappearance of notching of QRS after exercise. Twenty millimeter increase of QRS excursion after exercise.

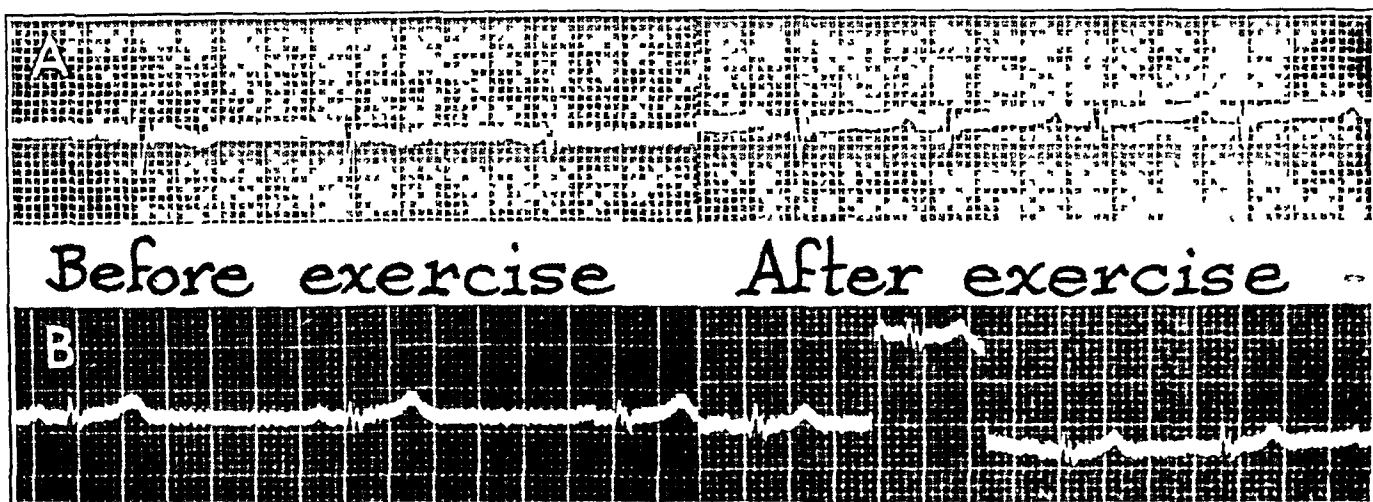


Fig 6—Leads I and III. Change in P wave and distortion of QRS complex. *I* shows increase in voltage of P after exercise and *B* distortion of QRS<sub>1</sub> in a normal young adult.

Distortion of the ST segment as the result of exercise has been reported as occurring in normal persons. In this study, however, distortion of ST or inversion of the T wave following exercise was found only in 3 persons who had clinical



T<sub>2</sub>, the phenomenon thus being found in all leads. In figures 3 and 4 are seen distortions of the ST segment which might easily be called evidence of possible myocardial damage but which disappear after three hard games of handball.

As with the T wave, the QRS complex presented some unusual but clinically insignificant variations from the normal. Figure 5 shows a feathering of the QRS complex produced by exercise and also a similar distortion in another subject which was present before exercise and which disappeared after one and one-half hours of handball. In figure 2 is seen a series of QRS complexes which



Fig 3—Leads I and II. Changes in ST segment and T wave. A, elevated take-off disappears after exercise in lead II and excursion of T wave decreases after exercise. B, T wave in lead I changes from positive to biphasic after exercise.

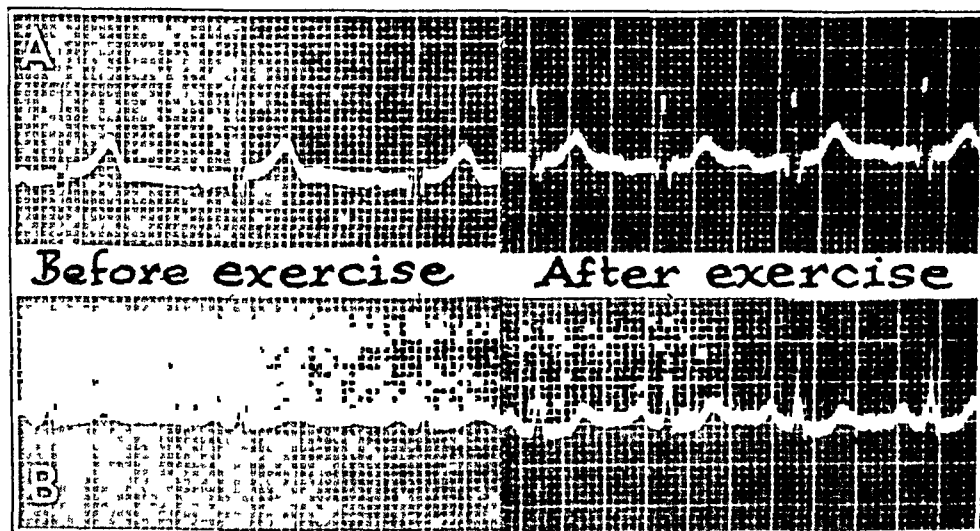


Fig 4—Leads III and CF<sub>4</sub>. Changes in QRS complex. A, decrease of excursion of QRS complex in lead CF<sub>4</sub> and notching after exercise (note also inversion of P wave after exercise and monophasic QRS complex in lead CF<sub>4</sub> in normal man). B, splintering of QRS<sub>3</sub> disappears on exercise.

vary in voltage after exercise. In normal persons the QRS complex in lead CF<sub>4</sub> is presumed to be biphasic. Figure 4, however, shows a monophasic and notched QRS complex in that lead in a tracing from a 43 year old handball player with a Schneider index above average, and contrary to the accepted standard these peculiarities were found in several other obviously normal persons. Figure 6 shows a small distorted QRS<sub>1</sub> in a tracing from a 23 year old boxer with a

# NIGHT CRAMPS AND QUININE

ABRAHAM GOOTNICK, M D

HINFS, ILL

A major task in geriatrics is management of manifestations of the degenerative changes peculiar to the aging process. Among these manifestations are two types of intermittent pain in the muscles of the lower extremities—the pain of intermittent claudication, and night cramps. The pathogenesis of intermittent claudication has come to be widely recognized, it is a pain of exercise, caused by inadequacy of blood supply in proportion to blood demand, much as is the anginal effort pain and like the latter it is an expression of organic or spastic narrowing of vessels carrying blood to the muscles involved.

The pain of night cramps, like the pain of claudication is intermittent, affects preponderantly the middle-aged and elderly and involves the same muscle groups. It is because of these obvious similarities that night cramps too have been generally considered a symptom of peripheral vascular disease. It is a common experience of specialists in vascular diseases to see patients with night cramps who have been referred for treatment of peripheral vascular insufficiency. This, almost uniformly, they do not have. What these patients all do show is some pathologic condition of the joints, nerves or ligaments of the lower extremities. The disorder may be a sciatic neuritis or a traumatic skeletal deformity, but the most frequent associated finding is chronic pathologic change in one or another of the weight-bearing joints.

The usual picture is that of a middle-aged man or woman who is free of muscle pain by day, whether resting or walking. He retires for the night without symptoms but is waked from sleep by an abrupt cramping pain in one or the other leg. On feeling the painful area he finds the muscles in hard contraction and tender. Vigorous rubbing of the calf muscles, hopping about or application of a hot towel causes gradual relaxation of the knotted muscle and relief from pain, but the area remains tender for a number of hours thereafter. The patient may return to sleep and be aroused repeatedly by recurring muscle cramps.

For a symptom so common and distressing, night cramps have attracted surprisingly little investigative attention. The incidence of night cramps in arthritic patients was studied by Pemberton,<sup>1</sup> who found that among patients with arthritis 32 per cent of the men and 43 per cent of the women had night cramps as a major complaint. A study by Pemberton and Foster<sup>2</sup> of the calcium-phosphorus metabolism in patients with arthritis long ago revealed that significant deviation from normal calcium balance does not occur in arthritis of either major type. My recent study<sup>3</sup> of calcium-phosphorus levels in sufferers from night cramps (of whatever cause) yielded uniformly normal values. The empiric administration to these patients of calcium salts in an effort to reverse a possible negative calcium balance proved of no value in alleviating the cramps.

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1 Pemberton, R. Arthritis and Rheumatoid Conditions. Philadelphia, Lea & Febiger, 1935, p. 53.

2 Pemberton, R., and Foster, G. L. Studies on Arthritis in the Army Based on Four Hundred Cases, Arch. Int. Med. 25:243 (March) 1920.

3 Unpublished data.

histories of cardiovascular disease, and who were not included in this series. We should therefore be suspicious of intrinsic myocardial damage when distortion of the ST segment or frank inversion of the T wave in significant leads is produced by exercise.

#### SUMMARY

With a series of 100 normal men a study was made of the electrocardiographic changes produced by vigorous participation in such active sports as handball and badminton. Tracings were taken immediately before and immediately after exercise.

There were no significant changes in the auriculoventricular or the intraventricular conduction time. Inversion of the P wave in lead  $CF_1$  after exercise occurred in about half the group. Changes in the T wave were limited to changes in voltage. These were common, but no frank inversion of the T wave or distortion of the ST segment was found. A change in the size of the QRS complex was most common, being found in four fifths of the men in the series.

Half of the men studied were under 40 years of age, with an average age of 31, while the other half were over 40, with an average age of 49. There were no significant electrocardiographic differences between the two age groups, although the incidence of change when it did occur was greater in the younger group.

Concurrently a determination of the Schneider index was made for each subject. There was no marked difference in the average rating of the two age groups. There was no demonstrable correlation between the Schneider index rating and the electrocardiographic changes noted with exercise.

Three fifths of the men studied were smokers. The smokers had a Schneider index slightly lower than the nonsmokers and changes in the P wave in lead  $CF_1$  and in the T wave were more frequent in this group. In the course of the investigation there were found a few distortions of I, SI and QRS which disappeared with vigorous and prolonged exercise and which may therefore be considered as occasional variants of the normal electrocardiogram.

Essentially, the mechanism of cramp in the leg muscles is the same as that of rigidity of the abdominal wall in the presence of visceral inflammation. It represents a variety of the segmental visceromotor reflex, except that here the irritative focus in the spinal cord is produced not by visceral disease but by change in skeletal structures of the same segmental distribution as the muscles affected. Again, the effectiveness of quinine here is due in part to its action directly on muscle tissue, but more important is its effect in interrupting the reflex arc, by blocking myoneural impulse transmission. Quinine acts, then, much as does digitalis in depressing the bundle of His in auricular fibrillation, by cutting down the number of impulses that can get through to stimulate the muscle to contraction.

Besides the predisposing factor of neighboring foci of irritation, there is another factor which precipitates the attacks and is responsible for the occurrence of cramps during the night rather than by day. The patient frequently volunteers that he can bring on a cramp at will, merely by extending his lower extremity. He may go to sleep with a pillow folded under his knee to keep it flexed and so attempt to ward off an attack of cramps. This is effective until he changes position in his sleep, straightens his leg and is seized with a cramp. The reason for this phenomenon is the physiologic fact that the tension of muscle fibers increases as the muscle lengthens.<sup>9</sup> Beyond a certain degree of lengthening, muscle, like a rubber band, acquires the tendency to recoil into spasm. During the day, with the patient in the erect or the sitting posture, the calf muscles maintain a considerable degree of tone and are in a state of partial contraction against varying degrees of pull. In the recumbent posture, however, relaxation and lengthening occur. In muscles already abnormally stimulated by impulses radiating from an irritated segment of the spinal cord, extension of the extremity constitutes a trigger mechanism sufficient to throw the stretched muscle group into spasm. This is really nothing more than an exaggeration of the myotatic or stretch reflex which is made use of every time the ankle jerk is elicited by tapping the achilles tendon. The sharp contraction of the gastrocnemius and soleus muscles in response to the momentary lengthening of their fibers by the blow of the hammer is accentuated and protracted many times over in response to their being stretched abruptly by the sleeping patient.

Tables 1 to 4 summarize observations on 30 patients suffering with night cramps. Although the majority sought help primarily for associated disabilities, night cramps were a troublesome symptom in all the patients, in 9 the cramps were the chief complaint. The grievance all had in common was the impossibility of sleeping through the night undisturbed. Three patients had been unable for many months to sleep except in an armchair, because going to bed meant a succession of painful spasms in the muscles of the calf. One man refused to undergo a laparotomy, giving as a reason his fear of postoperative evisceration. He felt certain that each time he fell asleep he would presently find himself out of bed, as was his wont, rubbing his knotted calf muscles before he was conscious enough to control his actions.

The lesions constituting the irritative foci included arthritis, hypertrophic or atrophic, of the weight-bearing joints, sciatic neuritis, deficiency states with peripheral neuritis of glove-stocking distribution, weak feet and traumatic residua with skeletal deformities throwing unusual strains on one or more joints. A case of muscular spasm due to traumatic strain (not included in this study) was that of a patient with irritation of the temporomandibular joint which followed the use of a new denture. For two weeks after he had finally discarded the denture, the

<sup>9</sup> Brown, D. The Regulation of Energy Exchange in Contracting Muscles, *Biol. Symposia* 3: 161, 1941.

The basis for the present effective treatment of night cramps was provided by Kennedy and Wolf,<sup>4</sup> who in 1937 described the disappearance of muscle spasm in myotonia under the influence of quinine. Reasoning that a drug effective against one type of muscle spasm might well work against other kinds of spasm, Moss and Herrmann<sup>5</sup> in 1940 gave quinine to 15 patients with night cramps, with uniformly successful results. While noting that night cramps do not seem to be related to peripheral vascular disease, the authors did not attempt to explain why night cramps occur.

To understand the mechanism of the night cramp and the action of quinine in relieving it, it is useful to review the relationship of two muscular disorders, myasthenia gravis and myotonia, and two antagonistic drugs, prostigmine and quinine. In myasthenia gravis, the essential fault is diminished irritability at the myoneural junction,<sup>6</sup> that is, decreased sensitiveness of the motor end plate to the acetylcholine which is the chemical mediator of impulse transmission at the synapse. This fault is enhanced by the giving of quinine,<sup>7</sup> which (1) increases the refractory period of the muscle fibers and (2) by impairing irritability at the myoneural junction decreases still further the number of stimuli that can reach the muscle fibers. In cases of early equivocal myasthenia, therefore, quinine has been diagnostically useful by quickening and making more evident the fatigability of the involved muscle groups.

As opposed to quinine, prostigmine promotes myoneural impulse transmission by destroying the enzyme choline esterase, which inactivates acetylcholine. In addition, it sensitizes the muscle fibers themselves to the action of acetylcholine. Hence the dramatic effectiveness of prostigmine in promptly abolishing the clinical manifestations of myasthenia gravis.

In myotonia the clinical manifestation is persistence of contraction in skeletal muscle after the end of voluntary stimulation. In abolishing this "after-contraction" or localized tetanus with quinine, Kennedy and Wolf<sup>4</sup> were making use of those properties of the drug just described: the ability of quinine to suppress repetitive muscle response by lengthening the refractory period and its curare-like depressing action at the myoneural junction.<sup>8</sup>

Night cramp in the lower extremity appears to be a lasting tetanic contraction of a muscle group due to reflex bombardment of the myoneural junctions by a stream of impulses from some neighboring source of irritation. This source of irritation may be arthritis in the hip or knee, weak feet or intrinsic inflammatory change in the nerves or muscles of the extremity. It is a fact frequently observed that as the irritative process in the skeletal structures subsides there is commensurate decrease in the frequency and severity of the muscle cramps. Conversely, aggravation of the irritative change, as by subjecting arthritic knees to long hours of weight bearing, is followed by noticeable intensification of the night cramps.

4 Kennedy, F., and Wolf, A. Experiments with Quinine and Prostigmin in Treatment of Myotonia Congenita, *Arch. Neurol. & Psychiat.* **37**: 68 (Jan.) 1937.

5 Moss, H. K., and Herrmann, L. G. Quinine for Relief of Night Cramps in the Extremities, *J. A. M. A.* **115**: 1358 (Oct. 19) 1940.

6 Harvey, A. M. Action of Quinine on Neuro-Muscular Transmission, *Bull. Johns Hopkins Hosp.* **66**: 1 (Jan.) 1940.

7 Harvey, A. M. Mechanism of Action of Quinine in Myotonia and Myasthenia, *J. A. M. A.* **112**: 1562 (April 22) 1939.

8 While the explanation given in these paragraphs is an obvious oversimplification of the physiology of neuromuscular impulse transmission, omitting among other factors the vital role of migration of potassium between muscle tissue and serum and the related effects of rest and exercise in myasthenic and myotonic states, it does help to illuminate the parallel relationships involved in night cramps.

In general this was the pattern of response to quinine medication. In 28 of the 30 patients including several who had not had a cramp-free night in months administration of the first capsule of quinine at bedtime dramatically abolished the spasms. Trial of various quantities of the drug led to the adoption of 3 grains (0.19 Gm) of quinine sulfate at bedtime as the optimal routine dose. For only 2 patients, 1 with severe sciatic neuritis and 1 with traumatic deformity of the foot, were larger doses (5 grains [0.32 Gm]) required to prevent the appearance of

TABLE 2—*Relation of Predisposing Irritative Source to Site of Cramps*

Patient	Irritative Focus	Muscles Cramped
P K	Arthritic knees	Calf muscles, bilateral
I B D	Arthritis of knees, ankles, ankylosis, right hip	Calf muscles, bilateral, right hamstrings
H J C	Traumatic deformity, left foot	Calf and intrinsic foot muscles, right only
A D	Peripheral neuritis, bilateral	Calf muscles, bilateral
L T W	Weak feet	Calf muscles, bilateral
H C S	Arthritis, lower spine	Calf muscles, bilateral
H McM	Weak feet	Calf and foot muscles, bilateral
J A P	Peripheral neuritis	Calf muscles, bilateral
R S V	Sciatic neuritis, left	Calf and hamstring muscles, left only
W B W	Arthritis of knees	Calf muscles, bilateral
A P	Arthritis of knees and ankles	Calf muscles, bilateral
C E B	Weak feet	Calf muscles, bilateral
J R	Sciatic neuritis, right	Calf muscles, right only
E R	Traumatic deformity, left foot	Calf muscles, left only
J F	Peripheral neuritis	Calf muscles, bilateral
E O W	Fibrositis of knees	Calf muscles, bilateral
E A F	Arthritis of spine, knees, etc	Calf muscles, bilateral
J M	Peripheral neuritis	Calf and foot muscles, bilateral
F J M	Arthritis of spine, hips, knees	Calf and hamstring muscles, bilateral
R D R	Arthritis of lower spine, hips	Calf muscles, bilateral
F M	Arthritis of spine, knees	Calf muscles, bilateral
J P K	Peripheral neuritis	Calf muscles, bilateral
H P	Sciatic neuritis, left	Calf and hamstring muscles, left only
P F	Weak feet	Calf muscles, bilateral
F C	Arthritis of spine, hips, knees, ankles	Calf and hamstring muscles, bilateral
H C	Weak feet	Calf muscles, bilateral
C T	Peripheral neuritis	Calf muscles, bilateral
H B	Weak feet	Calf muscles, bilateral
V V	Arthritis of spine, hips, knees, ankles	Calf muscles, bilateral
D G	Arthritis of spine, knees, ankles	Calf muscles, bilateral

TABLE 3—*Response to Initial Three-Grain Capsule of Quinine Sulfate at Bedtime*

Immediate abolition of cramps	28
Partial alleviation	2*
No response	0

\* Complete disappearance of cramps when dose was raised to 5 grains

TABLE 4—*Effect of Discontinuing Use of Quinine After Three Days\**

Immediate recurrence (the following night)	6
Recurred within three days	10
Recurred third to fifteenth day	5
No recurrence after a month or longer	3

\* Six patients left observation too soon to determine duration of relief

cramps, and then only temporarily. Even these 2 reported definite alleviation in the severity of the cramps after the initial 3 grain (0.19 Gm) dose.

A curious circumstance was that in several instances discontinuance of the use of the quinine capsule after three days was not followed by reappearance of the cramps the patient remaining free of them a week or more and sometimes indefinitely. As is well known, the effects of quinine and related derivatives are evanescent, most of the drug being excreted in the urine within thirty-six hours of ingestion. In controlling auricular fibrillation with quinidine, it is a common experience that a nightly dose may be necessary to prevent reappearance of the arrhythmia at breakfast time. In view of this, the prolonged relief from cramps

patient suffered agonizing trismus whenever he opened his mouth more than just enough to take a drinking tube. The masseter spasms disappeared after the first dose of quinine, and the patient was able to resume a soft diet without cramps

TABLE 1—*Pathologic Factors*

Patient	Age	Irritative Focus	Associated Conditions	Peripheral Vascular Status	Comment
P K	49	Atrophic arthritis, multiple joints	Secondary anemia	Normal	
I B D	47	Atrophic arthritis, multiple joints	Bronchial asthma	Mild angiospasm	
H J C	45	Traumatic deformity left foot	Cholecystitis	Angiospasm	Fewer cramps when alkaline powders stopped
A D	45	Deficiency polyneuritis	Tabs dorsalis (no Charcot joints)	Normal	
L T W	53	Weak feet	Leukemia	Normal	
H C S	52	Arthritis, lower spine	Duodenal ulcer	Normal	No cramps 1 week after quinine stopped given prostigmine ampules during roentgen series cramps that night only
H McM	52	Weak feet	Hypertension cardiac disease	Normal	
J A P	44	Deficiency polyneuritis	Malnutrition	Normal	
R S V	51	Sciatic neuritis	None	Angiospasm	
W B W	45	Arthritic knee	Cancer eye	Normal	
A P	57	Arthritic knees	Diabetes mellitus, obesity	Calcified peripheral vessels	
C L B	48	Weak feet	Leukemia	Normal	
J R	53	Sciatic neuritis	None	Normal	
E R	50	Traumatic deformity	Malnutrition	Angiospasm	
J F	44	Deficiency polyneuritis	Corvina	Normal	
I O W	54	Fibrositis, knees	None	Normal	
I A F	52	Hypertrophic arthritis, multiple joints	Duodenal ulcer	Normal	
I M	60	Deficiency polyneuritis	Generalized arteriosclerosis	Angiospasm	
I J M	44	Atrophic arthritis, multiple joints	Rheumatic cardiac disease	Angiospasm	
R D R	52	Arthritis, lower spine	None	Normal	
F M	53	Arthritic knees, spine etc	Duodenal ulcer	Normal	Fewer cramps after alkaline powders discontinued
J P K	55	Deficiency polyneuritis	Diabetes mellitus	Angiospasm	
H P	45	Sciatic neuritis	None	Normal	
P F	48	Weak feet	Recurrent appendicitis	Normal	
F C	51	Hypertrophic arthritis, multiple joints	Hypertension, cardiac disease, obesity	Angiospasm	
H C	63	Weak feet	Arteriosclerosis, cardiac disease	Normal	
O T	63	Deficiency polyneuritis	Pneumonia	Normal	
H B	52	Weak feet	Syphilis of the central nervous system	Normal	
V V	52	Hypertrophic arthritis, multiple joints	Hypertension, cardiac disease, prostatism	Calcified peripheral vessels	Prostigmine in course of roentgen studies caused recurrence of cramps, 1 night only
D G	38	Rheumatic arthritis, multiple joints	Rheumatic cardiac disease	Normal	

When, without the patient's knowledge, a capsule of acetylsalicylic acid was substituted on the fourth day, the trismus promptly reappeared and was again controlled with quinine

pregnant women There are, besides, numerous instances on record of pregnant women treated with full antimalarial doses of quinine who did not abort <sup>11</sup>

The tendency to muscle cramps in alkalosis was observed to play a part in 4 of the 30 patients These men had been on a regimen for peptic ulcer and had been treating themselves with considerable quantities of alkaline powders Before quinine was given, they were changed to a regimen which excluded alkaline medication Three of the 4 observed an appreciable diminution in severity and frequency of the cramps It would appear that in these men the disturbed acid-base balance had acted as a spasm-inducing factor in addition to the arthritis, by increasing further the irritability of the muscles

The muscle cramps of athletes may be of the immediate type, a manifestation of the marked hyperpnea of effort, and of the increased muscular irritability associated with the consequent elevation in  $p_H$  <sup>12</sup> Or they may be delayed and appear at night after a day of prolonged and strenuous exertion, particularly when previously little used muscles have been brought into play Here an evident myositis has developed (stiffness and tenderness of the muscles for days following), the inflammatory changes in the muscle proper constitute the irritative focus and play the same role as the older patient's inflamed joint or nerve

With injuries of long bones, the intense spasm of large muscle masses is probably more a matter of strong efferent stimulation from an irritated cord segment than a result of direct pressure of bone fragments This muscular spasm, which often presents a considerable problem in the management of fractures, should on theoretic grounds be just as responsive to adequate quinine medication as similar types of spasm already have proved to be

Tetanus and strychnine poisoning, of course, do their damage in the central nervous system primarily, still, their clinical effects are on the skeletal musculature The difference between other types of muscle spasm and the spasms in these two conditions is a difference of degree rather than of kind In tetanus and in strychnine poisoning the muscular activity is so widespread, so intense and so protracted that life processes, especially respiration, may be made impossible and the patient may die These two irritative states have this in common with the other varieties of muscle spasm previously mentioned, the stimulation of the muscles to contraction and the maintenance of the contracted state depend on nerve impulses originating centrally and reaching the muscle fibers across the myoneural junctions

Use of cinchona derivatives in man, by mouth and by vein, has already been tried extensively enough to demonstrate the safety and effectiveness of these drugs in controlling muscle spasm A notable example is the recent successful prevention of fractures in the course of convulsive therapy with metrazol <sup>13</sup> through the use of a synthetic quinine preparation There is therefore good reason to believe that the use of quinine as an antispasmodic drug may be extended to other generalized spastic states of the skeletal musculature A priori, so powerful an antitetanoid agent should be a decisive ally against strychnine poisoning and tetanus With the former the problem is to keep the victim alive long enough to allow elimination of the poison As for tetanus, the present accepted management depends on antitoxin and sedation The effects of antitoxin are limited by the fact that

11 Yorke, W., and Murgatroyd, F. *Malaria, Ann Trop Med & Parasitol* **25** 551, 1931

12 Best, C. H., and Taylor, N. B. *Physiologic Basis of Medical Practice*, Baltimore, William Wood & Company, 1937, p. 1101

13 Bennett, A. E., and Cash, P. T. *Curarization with Quinine Methochloride to Prevent Traumatic Complications of Metrazol Shock Therapy, Psychiatric Quart* **15** 351 (April) 1941



after discontinuance of quinine cannot be attributed to cumulative action of the drug. Rather, the tendency to cramps must be thought to have decreased below threshold level, on account of the rest and treatment accorded in the meantime to the predisposing irritative lesion.

The sex and age of the patients included in this study were predetermined by their being chosen from among veterans of World War I. From experience elsewhere, however, it is clear that the preponderant majority of sufferers from night cramps are persons in the fifth, sixth and seventh decades of life, the average age of a group culled from general practice closely approximates the average found here. As for sex distribution, the impressive frequency among women of post-menopausal obesity and articular changes more than offsets the greater incidence of traumatic arthritis and secondary sciatic neuritis in men. The present series then, is not to be taken as an indication of a greater incidence of night cramps among men.

The commonest single disorder predisposing to cramps in this group was arthritic change in the weight-bearing joints. There was no constant association of cramp in a particular muscle group with a corresponding site or type of arthritis. In a number of patients with cramps of the calf muscles the major pathologic condition was in the lumbosacral portion of the spine, rather than in the more distal joints. In the patients with weak feet, cramps in the calf muscles alternated on occasion with cramps in the intrinsic foot muscles. There was greater correspondence between irritative lesion and site of cramps in the patients with sciatic neuritis. In these the cramps were without exception restricted to the side of the inflamed nerve and involved usually the hamstring muscles as well as the calf muscles.

In none of the 30 patients did we find peripheral arterial disease of any importance. Moderate sclerosis of peripheral vessels was, as would be expected in persons of this age group, fairly common. In 2 men, an incidental observation in the roentgenograms of the joints was calcification of the coats of the popliteal and posterior tibial arteries. Eight patients had moderate peripheral angiospasm, manifested by some coldness of the feet and slight rubrocyanosis on dependency, in these men, too, however, the peripheral arteries were palpably pulsating and cutaneous nutrition was normal. Of the patients with angiospasm, all had normal vascular reserve; that is, they responded to a thermal stimulus with a normal degree of cutaneous vasodilation in the lower extremities.

#### COMMENT

An interesting consideration is the relationship of night cramps in the middle-aged and elderly to muscle cramps associated with other clinical disorders. In pregnancy, for instance, night cramps are a frequent complaint. Although the obvious mechanism which suggests itself is the tendency of the mother to have a negative calcium balance, the restriction of the cramps to the calf muscles and their occurrence in the last weeks of gestation point to the more likely hypothesis that pressure of the fetal head on the sacral nerves may be the source of irritation. Night cramps then develop in the same way as in the patients here described.

The therapeutic use of quinine in late pregnancy has been a matter of dispute among malariologists. There is good authority<sup>10</sup> for the belief that a 3 gram (0.19 Gm.) dose does not exert sufficient oxytocic effect, even on the gravid uterus, to endanger the pregnancy. The malaria inoculation treatment of dementia paralytica, with its concomitant use of quinine, is successfully administered to

<sup>10</sup> Manson-Bahr, P. H. Manson's Tropical Diseases, ed 10, Baltimore, William Wood & Company, 1936, p. 71.

# Progress in Internal Medicine

## LIVER AND BILIARY TRACT

A REVIEW OF THE LITERATURE FOR 1942

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NEW YORK

### JAUNDICE FOLLOWING VACCINATION FOR YELLOW FEVER

The laboratories of the International Health Division of the Rockefeller Foundation have been active since 1936 in the development and production of a vaccine which by a single injection provides active immunity of long duration against yellow fever <sup>1</sup>. As a result of the war emergency the demand for this vaccine has been so great as to require its production on an unprecedented scale.

The distribution of yellow fever vaccine manufactured by the Rockefeller Foundation in New York in 1941 <sup>2</sup> was as follows:

	Doses	
United States Army	959,300	
United States Navy	960,000	
United States Public Health Service	3,000	
Panama Canal Zone	4,000	
Virgin Islands	12,000	
	<hr/>	
Total for United States Government		1,938,300
West Africa	152,000	
South Africa	158,000	
East Africa	1,662,380	
	<hr/>	
Total for Africa		1,972,380
India	222,000	
Brazil	100,000	
Singapore	28,000	
	<hr/>	
Grand total		4,260,680

Great interest was aroused when it was reported by Army authorities in July that an epidemic of jaundice had developed among troops in the United States and abroad. This epidemic started in March and increased until a total of 28,585 cases was reported in July, when it was brought under control <sup>3</sup>.

Circular letter no. 95 from the Surgeon General's Office <sup>4</sup> reported that in this epidemic the clinical course of the disease had been remarkably uniform in the great majority of patients. The disease resembled most closely the so-called

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From the Clinic for the Study of Diseases of the Liver and Biliary Tract of the Departments of Medicine and Surgery, New York Post-Graduate Medical School and Hospital, Columbia University.

1 Fox, J. P., and Cabral, A. S. The Duration of Immunity Following Vaccination with the 17D Strain of Yellow Fever Virus, *Am J Hyg* **37** 93 (Jan.) 1943.

2 Fosdick, R. B. Report of the President of the Rockefeller Foundation for 1941-1942.

3 Jaundice Following Yellow Fever Vaccination, editorial, *J A M A* **119** 1110 (Aug. 1) 1942.

4 The Outbreak of Jaundice in the Army, Medicine and the War, *J A M A* **120** 51 (Sept. 5) 1942.

it cannot reach the toxin already combined with nerve tissue, it neutralizes only toxin elaborated at the wound and circulating in the blood. Heroic sedation, on the other hand, produces profound depression of the vital centers without accomplishing more than partial relaxation. It contributes materially to the incidence of a major cause of death in cases of tetanus, pulmonary complications.

What is badly needed with both conditions is the insulation for a number of days of the skeletal musculature against the ceaseless assault of stimuli from the central nervous system. The established pharmacologic capacity of quinine to interrupt the transmission of neuromuscular impulses, and its proved effect clinically against myotonia and night cramps suggest its probable value in the treatment of tetanus. In time of war, with tetanus inevitably on the increase, the use of a safe, well known and simply administered drug to hold in check the unremitting spasms is worthy of trial.

#### SUMMARY

A study of a group of 30 patients with night cramps is reported.

A theory of the mechanism of night cramps is offered and the effectiveness of quinine described.

Use of quinine to control muscular spasm in other clinical states, particularly tetanus and strychnine poisoning, is suggested.

system often showed changes similar to those found in it as a result of other severe toxic metabolic disturbances

It must be emphasized that the extensive damage observed in the rare fatal cases was not duplicated in the nonfatal cases. It is more than probable that "yellow or red atrophy" represents the extreme end of a scale of lesions on which there are many gradations from the usual slight and readily reparable injury, such as occurs in the average patient, to the extensive destruction of tissue in the one who succumbs. In those who died from accident or disease subsequent to an attack of jaundice, little or no evidence of preceding hepatic damage was found. All information available indicated that in the average patient the damage done to the liver was slight and repair prompt and complete.

Etiologic investigations, started in March, seemed to offer a promise that the jaundice-producing agent might be discovered ultimately. The results at the time of the initial public report had been negative as far as the demonstration of a transmissible agent was concerned. These negative results, however, served to exclude a number of infectious diseases in which jaundice occurs. The outbreak of jaundice in the Army was not Weil's disease or any other type of leptospiral infection. It was not a bacterial infection and had no relation to infectious mononucleosis. The disease was neither yellow fever nor a modified form of yellow fever. The virus of yellow fever was not recovered from any material (blood, bile, urine, liver) from jaundiced patients.

The search for the icterogenic agent or factors is progressing along two main lines. One of these is an attempt to transmit the disease with materials derived from patients. The other is an attempt to reproduce it in animals with yellow fever vaccine or its components. Experiments are being conducted with the whole vaccine, vaccine with lot numbers known to have been associated with a high incidence of jaundice being used. Vaccine with lot numbers not associated with jaundice is used as a control. On the assumption that the component of human serum in certain lots of vaccine administered up to April 18, 1942 may have carried an icterogenic agent, the donor lists are being analyzed, and experimental inoculations may be made with the blood of some persons who contributed pools of serum. It will probably be impossible to attack directly the question whether the chick embryo component carried the icterogenic agent. Factors involving the operation of an organ-specific (liver) antigen-antibody system are also being investigated.

Patients with jaundice occurring several weeks or longer after they were vaccinated against yellow fever have in their serum antibodies capable of neutralizing the virus. It is shown from tests that jaundice has occurred in persons immune to yellow fever. On the other hand, the serum of a jaundiced patient who has not been given an injection of yellow fever vaccine does not possess these virus-neutralizing properties. The immunologic studies strengthen the conviction that an agent other than the virus of yellow fever was the cause of the jaundice or that a process other than the contact of the vaccine virus with the hepatic cells was the cause of the pathologic changes in the liver.

Epidemics of hepatitis and jaundice with clinical and pathologic manifestations similar to those observed in the outbreak now ending have occurred among troops in the armies of many nations in the past. During the first year of the Civil War there were 10,929 reported cases with 40 deaths among Northern troops. The French have referred to the disease as the "jaundice of camps," and the English have often called it the "jaundice of campaigns." There were 2,195 persons with epidemic hepatitis among British troops in the Mesopotamian-Bairdanelles region from Sept 5 to Nov 6, 1915. It is a common enough disease of armies and

catarrhal jaundice or epidemic hepatitis of unknown cause. The onset was gradual, often imperceptible, until the appearance of jaundice. Increased susceptibility to fatigue, lassitude and anorexia were common prodromal or early symptoms, and in many cases, were the only symptoms. Nausea and vomiting occurred, and diarrhea sometimes preceded other symptoms. Fever was absent, or the temperature was but slightly elevated. The leukocyte count usually was normal, occasionally it showed a relative increase of monocytes. Pains in the joints and urticaria were present in about 20 per cent of cases. Dark-colored urine, yellow skin and scleras, and light-colored stools were usually noted. The liver was found to be enlarged and tender in about 20 per cent of cases. Bile pigments appeared in the urine and the blood. The icteric indexes ranged from 15 to 200, occasionally to 300. Prothrombin levels were reduced, and the excretion tests, such as the bromsulfalein test, indicated various degrees of disturbance of hepatic function. In most of the cases the disease was mild, and many cases were discovered only at special inspections. In a smaller but nevertheless considerable number the disease was more severe, with various stages of hepatic insufficiency being noted.

In general, recovery followed in four to eight weeks. In some stations convalescent camps were established to permit continuation of supervision of diet and activities in a regimen by which the patient was returned to duty gradually. Prognosis was favorable. Sufficient evidence is available to warrant the statement that recovery was complete in the vast majority of cases and that permanent damage of the liver occurred in only a few.

In the fatal cases of hepatitis observed during the year, death usually occurred from two to six weeks after the onset of the disease. The earlier stages of hepatitis were rarely observed by the pathologist. The chief pathologic lesions were those of an acute or subacute yellow or red atrophy of the liver. The earliest lesions consisted of frank necrosis of liver cells in the central parts of the lobules. Inclusion bodies were not present at any stage, the lesions thus differing distinctly from the lesions of yellow fever. Both the destructive process and the removal of debris by lysis were rapid. Within ten days the bulk of the necrotic material had usually been removed completely. The stroma was rarely damaged to any extent, in many areas the lobular framework remained intact. In most cases the destructive process was not diffuse, the severity of the damage tending to vary in different parts of the liver, in some areas the hepatic tissue was almost completely destroyed, whereas in others only the central parts of the lobules were necrotic. Unlike many forms of destructive hepatic diseases, this form did not have fatty changes as a conspicuous feature. Repair of the injured liver was brought about mainly by multiplication and hypertrophy of the remaining liver cells. The resulting lobules tended to be very large and were often of atypical construction. Destruction of liver tissue and removal of debris in this disease were invariably accompanied by inflammatory reaction, so that the term "hepatitis" is proper.

Changes in organs other than the liver were common. Of particular interest was the marked edema, often accompanied by intense inflammation, of the gastrointestinal tract. Although any part of the tract, including the esophagus, could be involved, the changes were usually most pronounced in the cecum. The relation of these lesions to the hepatitis was not determined. The kidneys presented the condition commonly known as biliary nephrosis (cholemic nephrosis). An acute or subacute splenic tumor usually was present. Hemorrhages, often extensive, in serous and mucous membranes were likewise common. The central nervous

in particular lots of vaccine and was not due to the virus of yellow fever used in the preparation of the vaccine, the method of preparation of the vaccine was changed and the epidemic of associated jaundice disappeared

While a great number of cases developed, the mortality was slight. Fortunately, it was possible to eliminate the unidentified causative factor. Even if this had not been possible, this complication was of little importance compared with the seriousness of yellow fever in unvaccinated patients

#### YELLOW FEVER

The foregoing observation is well emphasized by Soper,<sup>6</sup> as well as by Sawyer,<sup>7</sup> who summarized present knowledge of yellow fever in authoritative articles. They point out that yellow fever is a short, self-limited infection caused by a specific virus, followed by an intoxication due in large part to the destruction of tissue cells, especially the parenchymal cells of the liver

The clinical picture of yellow fever may vary as much as does that of measles, smallpox, poliomyelitis or any other virus disease. Yellow fever may be seen as

(a) An inapparent infection, recognized only through proof of acquired immunity

(b) An abortive infection with vague initial symptoms suggestive of mild influenza, lasting only some hours or possibly one day, often recognized only by slowing of the pulse during convalescence

(c) Incomplete attacks with severe onset, high fever, headache, body pains, dizziness and temperature and pulse curves typical of yellow fever but without hemorrhage, jaundice and anuria. Albuminuria and cylindruria may appear suddenly and increase rapidly on the third, fourth or even fifth day in the absence of other severe symptoms

(d) Complete attacks with classic yellow fever. Following a typical onset with symptoms of severe infection, there occur during the second stage albuminuria, hemorrhage and jaundice. The classic attack may be mild if the hemorrhage does not become excessive and the kidneys continue to secrete. Severe oliguria and anuria are found only in cases presenting hemorrhage and jaundice

The clinician notes in the early phase of classic yellow fever the usual signs and symptoms of acute infection but finds nothing to prepare him for the overwhelming intoxication which supervenes as the infection itself declines. The classic clinical picture of yellow fever is one of intoxication rather than of infection and consists of a symptom complex associated with the loss of hepatic and renal function, which is common to a number of diseases and intoxications producing destruction of hepatic parenchyma. This complex is not pathognomonic of yellow fever, it is the sequence of symptoms that is the most characteristic feature of the disease

*Period of Infection*—The onset of yellow fever is dramatic in the rapidity with which, within a period of a few hours, an apparently well person is transformed into a very sick patient. The symptoms—headache, backache, pain in the legs, malaise, nausea and vomiting—are out of all proportion to the physical findings. In many cases the infection is explosive; the pulse and the temperature reach their fastigia on the first day, after which there is a tendency for both to decline, the pulse falling sooner, more rapidly and more constantly than the temperature. This behavior of the pulse and the temperature is probably the most

<sup>6</sup> Soper, F. L. Treatment of Yellow Fever, J. A. M. A **118** 374 (Jan 31) 1942

<sup>7</sup> Sawyer, W. A. Yellow Fever, in Christian, H. A. Oxford Medicine, New York, Oxford University Press, 1939, vol. 5, pt. 2, pp. 731-738

camps of young adults in civilian institutions. Reports have been received of the occurrence of jaundice in British and German troops in Africa and in troops of the United Nations in the Middle East and in India. Outbreaks of jaundice in civilian communities in this country and abroad have been well described in the past and are also subjects of recent reports. That jaundice of the usual so-called catarrhal type may have occurred and may be occurring among troops of the Army of the United States in certain locations is unquestionable. Such outbreaks among troops and civilians are characterized by an incubation period of twenty to thirty-five days or less and a spread by contact. As stated, the number of cases of jaundice of this type in the Army appears to have been about 125 per month in the first two months of this year. No extensive outbreak of jaundice in the civil population has occurred in this country in the past year.

From an epidemiologic standpoint the present outbreaks of hepatitis and jaundice in the Army showed the following special features:

(1) Simultaneous occurrence in troops in locations widely separated, from the Pacific to the Atlantic and from the North to the South, with notable intermediate locations.

(2) Absence of demonstrable contacts between these units.

(3) Invariable association of all large and many small outbreaks with the administration of certain lots of yellow fever vaccine.

(4) Predictable occurrence of the jaundice in groups of persons, troop units and others known to have received these lots of vaccine.

(5) Predictable occurrence of a certain percentage of cases of jaundice at stations to which troops known to have received certain lots of vaccine were dispatched.

(6) Occurrence of a certain percentage of cases of hepatitis and jaundice after an incubation period of seventy to ninety days following the administration of the aforementioned lots of vaccine. This incubation period extended from about forty to one hundred and twenty days, depending on lot numbers and conditions to which the patients were exposed. A few cases occurred as long as six months after vaccination.

(7) Occurrence of large numbers of cases of jaundice in large groups of persons vaccinated with one or the other of these lots and occurrence of few cases "in instances in which subdivisions of the groups received these lots while the more numerous group of 'contacts' free from jaundice received other lots of vaccine or were not vaccinated against yellow fever."

(8) Absence, to date of Sept. 5, 1942, of secondary outbreaks in locations at which this type of jaundice occurred. This has been true of places in which there were large numbers of cases following yellow fever vaccination and of places in which the patients with postvaccinal jaundice were in the midst of many times their number of nonvaccinated persons or persons vaccinated with nonicterogenic lots.

Examples could be multiplied. They are the basis for the conclusion that this outbreak was a type of jaundice following the administration of certain lots of yellow fever vaccine. The disease was not contagious and hence did not constitute a danger to the public health.

This epidemic was not confined to the experience of the military personnel, for similar observations on icterus following vaccination for yellow fever were reported by Fox and his associates from Brazil.<sup>5</sup> Once it was recognized that the epidemic of postvaccinal jaundice was due to an agent present as a contaminant

<sup>5</sup> Fox, J. P., Manso, C., Penna, H. A., and Para, M. Observations on Occurrence of Icterus in Brazil Following Vaccination Against Yellow Fever. *Am J Hyg* **36**: 68 (July) 1942.

Studies on rhesus monkeys infected with yellow fever show the following early changes, which may appear some days before death: an increase in the bilirubin content of the blood, a decrease in the rate of excretion of bromsulfalein, a lowering of the fibrinogen content of the blood, associated with an increase in the clotting time. The later changes, generally apparent only on the last day before death, include progressive hypoglycemia, becoming severe in later stages, a high concentration of nonprotein nitrogen in the blood, an absolute increase in urea concentration, proportionately less than the increase in nonprotein nitrogen, an increase of amino acid nitrogen, proportionately greater than the increase of nonprotein nitrogen, an increase of test nitrogen. Creatinine increases but little, and that only immediately before death, probably as the result of terminal anuria, uric acid does not increase at all.

Only if yellow fever has produced obvious symptoms of intoxication do the concentrations of the nitrogenous constituents of the blood become appreciably altered. The most significant change is in the amino acid nitrogen, which shows strikingly large gains both absolutely and in relation to total nitrogen. The changes noted indicate a loss of ability to deaminate amino acids and to form urea, a deficiency of uric acid production and an impairment of the formation of hepatic glycogen, all of which are found following hepatectomy. It is difficult to escape the conclusion that they are dependent on destruction of the hepatic parenchyma. Although the kidneys are functionally damaged, the retention by the kidneys of the rhesus monkey of the ability to produce urine in normal amounts and normal concentration throughout the preintoxication stage of yellow fever indicates that this damage is not the chief factor in the production of the most characteristic disturbances of the disease. No definite evidence of serious impairment of renal function was observed except terminal anuria.

Autopsy generally reveals jaundice, hemorrhage, a pale yellow, fatty liver, a pale, flabby heart and tense, swollen kidneys. Greater or lesser evidence of hemorrhage may be found in the stomach, intestine, gallbladder, epicardium and pericardium, meninges, uterus, pleura, lungs and bladder.

*Microscopic Changes*—The most important microscopic lesions of yellow fever consist of degenerative changes (fatty degeneration and necrosis of the parenchyma) with almost no inflammatory reaction. Many organs and tissues are affected by these changes, but those of the liver, kidneys and heart are most important.

(a) *Liver* The extent of hepatic injury revealed by microscopic examination is surprising in the face of the relatively normal gross appearance of the liver. The degree of necrotic change may range from 5 to 95 per cent of the parenchymal cells. In extreme injury only a few cells recognizable as hepatic parenchyma may be found, some of these are seen close to the portal sheath at the periphery of the lobule, and a few others form a rim of scattered cells about the central vein. Fatty changes are always found, but the extent of involvement varies widely from patient to patient. There is no evidence of damage to the stroma.

(b) *Kidneys* The reaction of the kidneys to yellow fever is like that of the liver: degenerative, not inflammatory. The lesion varies greatly from cloudy swelling to severe fatty degeneration and necrosis and is not necessarily correlated with the alterations of renal function observed. The convoluted tubules of the cortex are especially subject to damage, but the medullary tubes may also suffer. The glomeruli may show congestion and some exfoliation of surface epithelium.

(c) *Heart* Well defined degenerative noninflammatory changes may be found in all parts of the myocardium. Granular and fatty degenerations of the muscular



constant and characteristic individual finding in yellow fever. Although the temperature often shows a secondary rise during the phase of intoxication, the pulse seldom does, in uncomplicated cases, except at death. Bradycardia is common after the third day.

The general picture presented by the patient during the period of infection is one of active congestion accompanied by severe prostration. Nausea and vomiting, associated with this period, are not necessarily indicative of a serious prognosis, and the early appearance of relatively heavy albuminuria is of diagnostic rather than prognostic importance.

Generally, at the end of the first forty-eight to seventy-two hours the congestion declines, the temperature reaches normal or even subnormal levels and the patient enters a period of relative tranquility, which marks the end of the period of infection.

*Period of Intoxication*—About the end of the third day, but sometimes as late as the fifth, the entire clinical picture changes. The active congestion of the previous period is replaced by venous congestion, accompanied by low arterial tension, nausea and vomiting, which may have been present during the period of infection, are now more severe and are of grave import. Overwhelming intoxication becomes apparent with the appearance of the formidable triad of albuminuria, hemorrhage and jaundice. In fulminant attacks the symptoms of intoxication are precocious and merge with those of the phase of the infection.

*Jaundice*—The jaundice may be so slight as to be missed by an inexperienced observer and is rarely or never intense in the early stages. Subicterus is the most common finding and may be noted in the conjunctivas as early as the end of the second day, but severe, visible cutaneous icterus appears late and is not found in the fulminant type of the disease in which symptoms of intoxication appear before those of infection have abated.

*Hemorrhage*—The amount of hemorrhage varies greatly, but some tendency toward hemorrhage is to be found in the majority of clinically diagnosable cases. Although slight hemorrhage may, and often does, occur during the initial stage of active congestion, the dangerous, typical hemorrhage of yellow fever is that of the second phase. Hemorrhage may be so severe as practically to exsanguinate the patient and is undoubtedly often the immediate cause of death.

*Proteinuria*—The onset of proteinuria is rapid, as if some sudden violent intoxication involving renal function had occurred rather early in the course of the infection. It is almost a constant finding in cases of yellow fever, and even cases of mild involvement will usually show some protein in the urine. Practically all cases of severe yellow fever show much heavier proteinuria than would be expected in severe fevers due to other causes.

Anuria, the most dreaded symptom, may occur unexpectedly in cases presenting an otherwise favorable prognosis. Anuria apparently depends on an entirely different mechanism from that producing precocious proteinuria. The former is never found without other signs of destruction of the liver, whereas the latter may be heavy in cases of mild disease without such signs. Anuria follows and seems to depend on hepatic involvement, proteinuria may precede and even be independent of other signs of hepatic intoxication. It is probably safe to conclude that proteinuria may occur either directly as a result of involvement of renal function during the phase of infection or later because of intoxication secondary to destruction of hepatic parenchyma but that anuria is produced only by this secondary intoxication.

to be of diagnostic aid in doubtful cases of jaundice. However, Jahn and Ludwig point out that the diagnosis of leptospirosis made by dark field examination should always be confirmed by animal inoculation or serologic tests before being accepted as conclusive.

#### INFECTIOUS AND TOXIC FORMS OF JAUNDICE

The various infectious and toxic forms of jaundice have been reviewed by Ottenberg and Spiegel<sup>17</sup>. They make a distinction between hepatic degeneration and jaundice due to infection and jaundice due to chemicals (table). The infectious forms of jaundice are again divided into groups depending on the nature of the hepatic degeneration—whether it is a dominant or an incidental feature of the clinical picture. Ottenberg summarizes an extensive literature and reemphasizes the observation that simple jaundice may progress to acute yellow atrophy. The chief difference between these two conditions is one of degree rather than of kind. The role of virus infections in both conditions is stressed, as is the probability that several different viruses may produce this clinical picture. While the gross similarities in the clinical pictures of the various types of infectious jaundice are well known, Ottenberg calls attention to the latent period before the appearance of the jaundice in epidemic acute yellow atrophy, yellow fever and leptospirosis. A similar latent period is observed after the introduction of some chemical poisons. Following recovery, a specific immunity is observed in the various types of infectious jaundice. In contrast, after recovery from chemical jaundice there is a greater sensitivity to many hepatotoxic agents.

Hepatic parenchymal diseases are classified by Ottenberg and Spiegel<sup>17</sup> as follows:

- I Infections causing degeneration of the liver and jaundice
  - A Infections in which hepatic degeneration is a dominant feature
    - 1 (a) Simple jaundice, (b) acute yellow atrophy
    - 2 Leptospirosis
    - 3 Yellow fever
  - B General infections associated occasionally with jaundice
    - 1 Lobar pneumonia
    - 2 General septicemia
    - 3 Syphilis
    - 4 Tuberculosis
    - 5 Acute infectious mononucleosis
    - 6 Malaria
    - 7 Oroya fever
- II Jaundice due to chemicals
  - A Direct injury to liver parenchyma
    - 1 Therapeutic agents gold, chloroform, arsenic, carbon tetrachloride, ether, iodoform, avertin, etc
    - 2 Accidental contacts amanitotoxin, nitrobenzene, phosphorus, burns, etc
    - 3 Industrial hazards tetrachlorethane, carbon disulfide, trinitrotoluene, etc
    - 4 Experimental agents selenium, copper, etc
  - B Primary hemolysis with secondary injury to the liver cells
    - 1 Therapeutic agents phenylhydrazine, sulfonamide compounds, incompatible blood in transfusions
    - 2 Accidental contacts snake poison, bean poison
    - 3 Industrial hazard arsine
    - 4 Experimental agents distilled water, toluendiamine
  - C Idiosyncrasy, hypersusceptibility and allergic sensitivity
    - 1 Therapeutic agents arsphenamine, cinchophen, liver extract, bismuth, sulfonamide compounds, mercury

<sup>17</sup> Ottenberg, R, and Spiegel, R. The Present Status of Non-Obstructive Jaundice Due to Infectious and Chemical Agents, *Medicine* **22** 27 (Feb.) 1943

fibers are constantly found, hyaline and vacuolar degenerations less frequently. The degenerative lesions of the myocardium are sufficient to explain the functional disturbances encountered in yellow fever, such as bradycardia, lowered arterial pressure, severe asthenia, venous stasis and electrocardiographic irregularities.

The lesions are not equally severe in all organs of the same patient. When the liver is badly damaged, the heart may escape lightly, or vice versa, while in other instances the kidneys seem to bear the brunt of the attack. There is, however, in all cases resulting in death an appreciable necrosis of liver tissue, and this is the most constant as well as the most characteristic lesion of yellow fever.

*Prophylaxis*—Soper stresses the necessity of achieving prophylaxis both by the eradication of yellow fever mosquitoes and by vaccination with the production of active immunity. According to tests, the immunity has lasted unchanged for the four year period since the present vaccine was introduced. Prophylaxis is important, for there is no specific treatment. Instead Soper quotes the aphorism of the Brazilian authority Sinval Lins<sup>8</sup>: "The therapy of yellow fever can be given in a single line—The disease cures itself or kills in spite of any and every treatment."

The difficulty in differentiating yellow fever from other types of jaundice and the presence of the latter in tropical areas are emphasized by Smith,<sup>9</sup> who reports a series of 14 cases of jaundice occurring in West Africa. The clinical findings in these cases suggested the diagnosis of yellow fever but the microscopic examination of the liver made it possible to exclude the latter diagnosis.

#### LEPTOSPIROSIS ICTEROHAEMORRHAGICA

Leptospiral jaundice (Weil's disease) was confused with yellow fever in the early days of the search for the causative agent of yellow fever. The two diseases are now readily distinguishable by laboratory methods. Cases of leptospiral jaundice (Weil's disease) continue to be recognized and reported in this country in increasing numbers. Wilen, Snively and Bruno<sup>10</sup> and Durand<sup>11</sup> have reported cases from New Orleans. Lester and his associates<sup>12</sup> have described a group of 14 cases from a coal mine in Alabama. Two have been reported from Philadelphia by Kramer<sup>13</sup> and 10 from New York by Tiffany and Martorana.<sup>14</sup>

The importance of agglutination tests in the identification of the disease is stressed by Packhamian<sup>15</sup> and by Tiffany and Martorana.<sup>14</sup> Jahn and Ludwig<sup>16</sup> have reported a case in which dark field examination of the blood showed leptospiral bodies. Many more organisms were found in the duodenal drainage, where they persisted until the twentieth day of the disease. This observation promises

<sup>8</sup> Lins, S, cited by Soper.<sup>6</sup>

<sup>9</sup> Smith, E C. Hepatic Findings Excluding Yellow Fever in Fourteen Cases of Jaundice in West Africa, *Ann Trop Med* **36** 38 (June 30) 1942.

<sup>10</sup> Wilen, C J, Snively, J R, and Bruno, F E. Report on Recently Observed Cases of Weil's Disease, *New Orleans M & S J* **94** 338 (Jan) 1942.

<sup>11</sup> Durand, J A. Weil's Disease (Spirochetal Jaundice), *New Orleans M & S J* **94** 341 (Jan) 1942.

<sup>12</sup> Lester, B S, Denison, G A, Posey, L C, and Tate, G M. Weil's Disease. Clinical and Epidemiological Report of Fourteen Cases, *South M J* **35** 325 (April) 1942.

<sup>13</sup> Kramer, D W. Weil's Disease. Incidence, Diagnosis and Treatment, Report of Two Cases, *Pennsylvania M J* **45** 1298 (Sept) 1942.

<sup>14</sup> Tiffany, E J, and Martorana, N F. Leptospirosis in New York City. Serological Survey, *Am J Hyg* **36** 195 (Sept) 1942.

<sup>15</sup> Packhamian, A. Positive Agglutination Tests in Suspected Cases of Weil's Disease, *Pub Health Rep* **56** 2145 (Nov 7) 1941.

<sup>16</sup> Jahn, F, and Ludwig, E. Demonstration of Spirochetes by Means of Dark Field in Duodenal Juice in Weil's Disease, *Deut Militararzt* **6** 274 (May) 1941.

ascites and hemorrhage and in the symptomatic management of ascites and of portal cirrhosis are reviewed by Greene<sup>21</sup> The indications for administration of mercurial diuretics with added acid salts, such as ammonium chloride or ammonium nitrate, for paracentesis, for giving liver extract, for transfusions, for vitamin K therapy and for omentopexy are discussed He reports that in selected cases infusions of ascitic fluid seemed to have some value in conserving plasma protein and in treating hypoproteinemia

The greater part of the earlier literature on the experimental production of hepatic cirrhosis by dietary measures was reviewed last year<sup>21</sup> Further experiments have been reported by Daft, Sebrell and Lillie and their associates,<sup>22</sup> showing that in rats neither a high fat diet nor one containing free cystine was essential for the production of hepatic cirrhosis They found that choline, methionine or casein in sufficient amounts would prevent the development of cirrhosis or, if given after the cirrhosis had developed, would favor regeneration of hepatic cells and improvement in the clinical condition of the animals These experiments therefore parallel the clinical observation of Broun and Muether<sup>23</sup>

#### THE LIVER IN RELATION TO PROTEIN METABOLISM

The relation of the liver to protein metabolism has long been recognized, but knowledge regarding details is increasing rapidly at the present time The paramount role of the liver in the deamination of amino acids and the synthesis of urea is well known The part played by the liver in the synthesis of serum proteins, especially of serum albumin, and the association of hypoalbuminemia with hepatic cirrhosis are recognized<sup>24</sup> The effects of high protein diets in protecting the liver from toxic injury by such substances as chloroform and in preventing cirrhotic changes in experimental animals on special diets have been discussed

Evidence has gradually been accumulated to show that the body contains considerable stores of protein and that the liver is one of the principal storehouses This was suggested by Pfluger<sup>25</sup> and Seitz<sup>26</sup> and demonstrated by Addis and his associates<sup>27</sup> and by Luck<sup>28</sup> The reserve stores of protein in the liver are increased by a high protein diet and decreased by fasting According to Addis,

21 Greene, C H Physiological Considerations in the Treatment of Portal Cirrhosis, *J A M A* **121** 715 (March 6) 1943, Liver and Biliary Tract A Review for 1941, *Arch Int Med* **69** 691 (April) 1942

22 Daft, F S, Sebrell, W H, and Lillie, R D Prevention by Cystine or Methionine of Hemorrhage and Necrosis of the Liver in Rats, *Proc Soc Exper Biol & Med* **50** 1 (May) 1942 Lowry, J V, Daft, F S, Sebrell, W H, Ashburn, L L, and Lillie, R D Treatment of Dietary Liver Cirrhosis in Rats with Choline and Casein, *Pub Health Rep* **56** 2216 (Nov 14) 1941 Lillie, R D, Ashburn, L L, Sebrell, W H, Daft, F S, and Lowry, J V Histogenesis and Repair of the Hepatic Cirrhosis in Rats Produced on Low Protein Diets and Preventable with Choline, *ibid* **57** 502 (April 3) 1942

23 Broun, G O, and Muether, R O Treatment of Hepatic Cirrhosis with Choline Chloride and Diet Low in Fat and Cholesterol, *J A M A* **118** 1403 (April 18) 1942

24 Post, J, and Patek, A J, Jr Serum Proteins in Cirrhosis of the Liver I Relation to Prognosis and Formation of Ascites, *Arch Int Med* **69** 67 (Jan) 1942, II Nitrogen Balance Studies on Five Patients, *ibid* **69** 83 (Jan) 1942

25 Pfluger, E Glykogen, *Arch f d ges Physiol* **96** 1, 1903

26 Seitz, E Die Leber als Worrathskammer fur Eiweisstoffe, *Arch f d ges Physiol* **111** 309, 1906

27 Addis, T, Lee, D D, Lew, W, and Poo, L J The Protein Content of the Organs and Tissues at Different Levels of Protein Consumption, *J Nutrition* **19** 199 (Feb) 1940 Addis, T, Poo, L J, and Lew, W The Quantities of Protein Lost by Various Organs and Tissues of the Body During a Fast, *J Biol Chem* **115** 111 (Aug) 1936

28 Luck, J M Proteins I The Question of Protein Storage, *J Biol Chem* **115** 491 (Sept) 1936

## PORTAL CIRRHOSIS

A comprehensive study of portal cirrhosis has been reported by Ratnoff and Patek<sup>18</sup> Records of 386 patients from various New York hospitals were analyzed with reference to the presence of antecedent factors, the chief symptoms and signs, the complications of cirrhosis, the prognosis as to life after the development of specific signs and the causes of death In addition they give a critical review of much of the pertinent medical literature

In this survey they found an increased incidence of cirrhosis in patients of Italian and Irish stock, though there was no convincing evidence of hereditary predisposition Characteristically it appears in late middle life (40 to 65 years) Men were affected two to three times as often as women, perhaps because of the greater frequency of alcoholism in men A study of dietary factors emphasized the importance of an antecedent deficiency to which the alcoholism may well have contributed In a smaller group of cases syphilis, exposure to arsenic, malaria, typhoid and paratyphoid fevers, acute hepatitis and thyroid disease appeared to be possible contributory factors

The initial clinical symptoms usually were flatulent dyspepsia and swelling of the abdomen Loss of weight was the most frequent symptom and occurred in one half of the cases Hematemesis occurred in about one quarter of the group The frequency of other signs is presented in detail

The chief signs of portal cirrhosis were ascites, edema, jaundice a palpability of the liver or spleen, fever and evidences of collateral circulation The role of portal hypertension and of a reduction in the serum albumin in the production of ascites was discussed Jaundice frequently was a terminal phenomenon Ratnoff and Patek stress the frequency of peripheral neuritis and its relationship to associated nutritional deficiencies

Ascites, jaundice and hematemesis were all of serious prognostic import Because of the size of the series it was possible for these authors to publish survivorship curves, showing the survival after the onset of each of these events In each instance less than one third of the patients survived the first years

The immediate cause of death was hepatic failure or cholemia in 35 per cent of the cases This usually was accompanied by jaundice Hematemesis was the terminal episode in one fourth of the cases In another quarter of the cases death was due to secondary infections

The treatment of cirrhosis by high vitamin high protein, low fat diets is discussed by Patek and Post<sup>19</sup> and by Fleming and Snell<sup>20</sup> Both groups of investigators report encouraging results in their series of cases Not only was the clinical course of the disease influenced favorably but there was an increased period of survival in the treated as compared with the control groups of patients While the results were encouraging, it must be remembered that the effects were slow It took time for improvement in nutrition as well as for regeneration of hepatic tissue

The dietary treatment of patients with cirrhosis therefore represents only one phase of the management of the condition The various factors in the control of

18 Ratnoff, O D, and Patek, A J, Jr The Natural History of Laennec's Cirrhosis of the Liver An Analysis of Three Hundred and Eighty-Six Cases, *Medicine* **21** 207 (Sept) 1942

19 Patek, A J, Jr, and Post, J Treatment of Cirrhosis of the Liver by a Nutritious Diet and Supplements Rich in Vitamin B Complex, *J Clin Investigation* **20** 481 (Sept) 1941

20 Fleming, R G, and Snell A M Portal Cirrhosis with Ascites An Analysis of Two Hundred Cases with Especial Reference to Prognosis and Treatment, *Am J Digest Dis* **9** 115 (April) 1942

injected intravenously into these animals the retention of these substances was proportional to the decrease in the serum albumin. Goettsch and her associates interpret this as evidence of impairment of hepatic function. Changes of equal severity are not likely to be seen clinically for Stewart and Rourke<sup>34</sup> found that intravenous infusions of amino acid mixtures were equally well utilized by normal persons and by patients with various diseases of the liver and biliary tract.

Fagin and Zinn<sup>35</sup> report good results in 5 patients with hepatic cirrhosis who received amino acid mixtures intravenously. No controls were used, so that it is not possible to decide whether these beneficial responses were due to the amino acid mixtures or to the general measures which were undertaken at the same time. The work of Goettsch and her associates and that of Post and Patek have suggested that the severely damaged liver cannot utilize amino acids at a normal rate, whether these are parenteral or digestive in origin. Response to therapy then must depend on improvement in the general nutritional condition of the patient rather than on a specific effect of the injected amino acids.

#### THE MANAGEMENT OF THE TYPHOID CARRIER

The control of typhoid fever in many states has reached the point where contaminated water, milk and food no longer are of significance in the spread of the disease. Under these conditions carriers of typhoid bacilli become the chief factor in the maintenance of the infection. Control of these carriers is therefore of paramount importance to public health. The carriers may harbor the bacilli in the gallbladder, the biliary ducts, the intestine or the urinary tract. Biliary carriers are the most frequent and can be recognized by culturing the bacilli from the duodenal drainage.

To date no satisfactory biliary antiseptic has been reported. Hanssen<sup>36</sup> summarized the findings in this field in 1939 and reported that cholecystectomy was the most successful method of eradicating the carrier state. He reported cure in 85 per cent of 160 cases collected from the literature. Additional cases have since been reported by Elsom and her associates<sup>37</sup> and by Collier and Crabtree<sup>38</sup> among others. Elsom reported that roentgen therapy was entirely ineffective in eradicating the infection.

Tetraiodophthalein sodium was shown by Nickel<sup>39</sup> to have some bacteriostatic action. Onodera and his associates<sup>40</sup> and Saphir and Howell<sup>41</sup> later reported

33 Goettsch, E., Lyttle, J. D., Grim, W. M., and Dunbar, P. Amino Acid Studies I. Plasma Amino Acid Retention in the Hypoproteinemia Dog as Evidence of Impaired Liver Function, *J. Biol. Chem.* **144** 121 (June) 1942.

34 Stewart, J. D., and Rourke, G. M. Changes in Blood and Urine After Intravenous Amino Acid Mixture in Patients with Liver Disease, *Proc. Soc. Exper. Biol. & Med.* **51** 364 (Dec.) 1942.

35 Fagin, I. D., and Zinn, F. T. Cirrhosis of the Liver. Results of Treatment with Parenterally Administered Amino Acids, *J. Lab. & Clin. Med.* **27** 1400 (Aug.) 1942.

36 Hanssen, E. C. The Present Status of the Typhoid Carrier Problem, *New York State J. Med.* **39** 1347 (July 15) 1939.

37 Elsom, K. O'S., Miller, S. G., Forrester, J. S., and Chamberlin, G. W. Radiation and Cholecystectomy as Therapeutic Procedures for Typhoid Carriers, *Am. J. M. Sc.* **194** 466 (Oct.) 1937.

38 Collier, F. A., and Crabtree, P. Chronic Biliary Typhoid Carriers, *Surgery* **12** 426 (Sept.) 1942.

39 Nickel, A. C. Tetraiodophthalein Sodium—N. N. R. (Tetraiodophenolphthalein) as an Antiseptic and Germicide of the Biliary Tract, *J. Pharmacol. & Exper. Therap.* **37** 359 (Nov.) 1929.

the gain or the loss may amount to some 40 per cent of the protein in the liver. The accumulated evidence on this topic was reviewed by Luck in 1938<sup>29</sup>

Since then Elman and Heifitz<sup>30</sup> have shown that when dogs are made hypoproteinemic by a protein-deficient diet, the protein content of the liver is reduced. Histologic changes in the liver could be correlated with the reduction in the protein.

More recently Elman, Smith and Sachar<sup>31</sup> have reported that following protein starvation the histologic appearance of the liver, as well as its content of nitrogen and glycogen, depends on the intake of carbohydrate. When the intake of carbohydrate is high, the cells are large, contain little protein and present a rarefied appearance of the cell cytoplasm often called hydropic degeneration.

After a fast (absence of carbohydrate), the liver is just as deficient in total nitrogen because it is smaller although the concentration thereof is normal. The microscopic picture may be called one of atrophy. The cells are smaller, the nuclei closer together and the cytoplasm dense.

These observations are significant in showing the magnitude of the changes in the cytologic appearance of the liver in consequence of differences in diet, with resultant changes in the size and the chemical composition of the liver. The role of similar changes in the chemical composition of the liver must be kept in mind in interpreting the appearance of pathologic sections.

Interpretations such as this are based on the assumption that the hepatic cell consists of a unit of protoplasm that represents the basal protoplasmic constituents essential to life and continued function of the cell. Superimposed on this basic material are reserves or stores of protein, fat and glycogen possibly with varying amounts of bound water. So far no investigator has been able to determine these different materials with accuracy. Until that can be done, the interpretation of changes in the chemical composition of the liver is difficult because it is not possible to decide whether the percentage changes are due solely to shifts in the amounts of stored reserves or are due also to changes in the number of parenchymal cells. The use of colonies of rats of uniform age and size will permit statistical analysis of changes in the gram weight of the liver and give a quantitative measure of the total changes found. But until this is combined with a measure of the protoplasmic units, complete analysis is not possible.

For many years a satisfactory parenteral method of supplying protein to the body has been sought. This problem has apparently been solved in two ways. One way is by the use of blood plasma. The benefit of plasma in preventing wound shock has been one of the outstanding developments of military medicine in the present war. Plasma, however, is expensive and without the pressure of the wartime emergency, it would not be so readily obtainable. Various protein digests have been studied, and it has been shown that a patient can be kept in nitrogen equilibrium by intravenous injection of amino acids. The extensive literature on this topic has been reviewed by Martin and Thompson<sup>32</sup> in detail. Most of the literature has dealt with the use of this therapy in various medical and surgical conditions. Goettsch, Lyttle, Grim and Dunbar<sup>33</sup> found that in dogs fed a very low protein diet a progressive hypoproteinemia developed. When amino acids were

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29 Luck, J. M. *The Liver Proteins*, in Needham, J., and Green, D. E. *Perspectives in Biochemistry*, London, Cambridge University Press, 1938.

30 Elman, R., and Heifitz, C. J. *Experimental Hypoalbuminemia*, *J. Exper. Med.* **73** 417 (March) 1941.

31 Elman, R., Smith, M. G., and Sachar, L. A. *Correlation of Cytological with Chemical Changes in the Liver as Influenced by Diet, Particularly Protein*, *Gastroenterology* **1** 24 (Jan) 1943.

32 Martin, G. J., and Thompson, M. R. *Intravenous Alimentation with Amino Acids*, *Medicine* **22** 73 (Feb) 1943.

without first establishing the condition of the gallbladder and biliary tract is irrational and uneconomical, for only a small proportion of carriers of typhoid are really suitable for such a trial

#### DISEASE OF THE GALLBLADDER

Various discussions of chronic cholecystitis have appeared, but no attempt will be made to review those dealing with surgical statistics or the general features of chronic cholecystitis. The tendency rather has been to emphasize the importance of biliary dyspepsia, as in the article of Holroyd<sup>49</sup>. A similar point of view is held by Moser and his associates,<sup>50</sup> who point out that the colic of gallbladder disease usually is relieved by cholecystectomy but that the dyspepsia is not. They insist, therefore, that dyspepsia alone should not be an indication for cholecystectomy.

Similar discussions relative to disturbances in the common duct have been presented by Best<sup>51</sup> and Wilensky<sup>52</sup>. The most comprehensive survey of gallbladder disease is that of Russell, Carter and Oppenheim,<sup>53</sup> who discuss the cause, the diagnosis and the treatment of diseases of the gallbladder in detail. In this discussion they have introduced several concepts not ordinarily considered.

The usual point of view, as presented for example by Walters and Snell,<sup>54</sup> is that

no form of cholecystic disease, gallstones in particular, appears as a primary disorder, there must be an initial injury to the structure of the gallbladder, which in turn may develop to the point of complete functional incapacity, formation of stone or state of chronic infection, present individually or in combination. The nature of these hypothetical initial injuries never has been satisfactorily determined, one or several factors may be responsible. There is much to suggest that the typical stone-bearing functionless and infected gallbladder seen by the surgeon at operation may have arrived at its condition by any one of several different routes. Once the normal physiologic properties of the gallbladder have been disturbed a host of factors pertaining to infection, motor disturbances and alterations in the chemical constituents of the bile may become operative to perpetuate and advance a pathologic process. For the aforementioned reasons it is necessary to consider first the mechanisms by which the initial damage is done and then to examine the evidence bearing on the further development of the pathologic process.

The subject of initial injury to the gallbladder may be considered from the standpoint of (1) infection, (2) disturbances in cholesterol metabolism produced in various ways, and (3) mechanical, toxic and chemical factors.

Russell, Carter and Oppenheim<sup>53</sup> attempt to define this initial factor and have sought for the earliest evidence thereof. They find that anatomic and physiologic abnormalities frequently precede and serve as a basis on which disease processes develop. They therefore look on gallstones, infection and cholecystitis as organic lesions developing on an underlying disturbance in structure or function. Treatment, to be successful, must be directed toward the basic functional disturbance as well as toward the engrafted organic complication.

They therefore emphasize that disease of the gallbladder is progressive. Whatever the initiating process, be it functional or organic, time adds factors such as gallstones, infection, obstruction or obliteration of the gallbladder. If the

49 Holroyd, F. J. Biliary Dyskinesia, *West Virginia M. J.* **37** 407 (Sept.) 1941.

50 Moser, R. H., Rosenak, B. D., and Hasterlik, R. J. Gallbladder Dyspepsia, *Am. J. Digest. Dis. & Nutrition* **9** 49 (Feb.) 1942.

51 Best, R. R. Management of Common Duct Lesions, *Nebraska M. J.* **26** 5 (Jan.) 1941.

52 Wilensky, A. O. The Danger of Procrastination in Biliary Tract Disease Until Irreversible Liver and Kidney Changes Occur, *Am. J. M. Sc.* **203** 231 (Feb.) 1942.

53 Russell, T. H., Carter, R. F., and Oppenheim, E. Gallbladder Disease. Etiology, Diagnosis and Treatment, *Bull. New York Acad. Med.* **19** 77 (Feb.) 1943.

54 Walters, W., and Snell, A. M. Diseases of the Gallbladder and Bile Ducts, Philadelphia, W. B. Saunders Company, 1940.



a germicidal action of soluble iodophthalein (tetraiodophenolphthalein sodium) on the typhoid bacillus Saphir and Howell reported a carrier of paratyphoid bacilli and Enright<sup>42</sup> a carrier of typhoid bacilli apparently cured by treatment with soluble iodophthalein Saphir, Baer and Plotke<sup>43</sup> continued these studies on a series of 110 carriers of typhoid bacilli Sixty-five of these were established to be biliary carriers In 21 of these, or one third, cultures of the duodenal drainage became negative after treatment The carrier state, however, was not cured, for an intestinal carrier state was present in the majority of instances Only 76 per cent of the persons studied were cured of their carrier state by treatment with soluble iodophthalein

Cutting and Robson<sup>44</sup> have reported a series of 6 carriers of typhoid bacilli and 1 carrier of dysentery bacilli who were not cured by treatment with thionol (3-oxo-7-hydroxy-3-isophenothiazine), phenothiazine, soluble iodophthalein, sulfaguanidine (sulfamylguanidine) or sulfadiazine (2-[paraaminobenzenesulfonamido]-pyrimidine) Ames<sup>45</sup> also has reported a series of 8 carriers of typhoid bacilli treated with soluble iodophthalein without success

The treatment of the carrier of typhoid bacilli with sulfaguanidine was initially advocated by Levi and Willen<sup>46</sup> They administered this drug to a carrier who had typhoid bacilli in both the biliary and the intestinal tract and who continued to have positive cultures of the stools after cholecystectomy The continuous administration of sulfaguanidine for a week apparently cured this carrier The effectiveness of sulfaguanidine could not be confirmed by Saphir, Baer and Plotke<sup>43</sup> or by Cutting and Robson<sup>44</sup> Hoagland,<sup>47</sup> however, has reported successful results in 2 cases He points out that sulfaguanidine can be effective only in intestinal carriers The value of this compound in the treatment of intestinal typhoid bacillus carriers is still undecided, but the need for careful selection of the patients in which it is to be tried is apparent

It is evident, therefore, that at present there is no dependable or efficient curative agent for the eradication of the typhoid carrier state Control of the carrier by established methods must continue This rule applies to the biliary carrier as well as to the carrier in whom the exact locus of the bacilli has not been determined However, the reviewer agrees with Saphir, Baer and Plotke<sup>43</sup> that when a carrier shows typhoid bacilli in the bile obtained by duodenal drainage, and cholecystograms show a normally functioning gallbladder without stones, a trial of soluble iodophthalein is indicated Treatment with soluble iodophthalein

40 Onodera, N, Murakawa, G, and Liu, S Ueber eine neue Behandlung von Typhus Bazillenträgern, *Deutsches Arch f klin Med* **171** 503, 1931

41 Saphir, W, and Howell, K M Soluble Iodophthalein in Treatment of Carriers of Typhoid Paratyphoid Group, *J A M A* **117** 1988 (May 18) 1940

42 Enright, J R Apparent Cure of a Typhoid Carrier with Soluble Iodophthalein, *J A M A* **116** 220 (Jan 18) 1941

43 Saphir, W, Baer, W H, and Plotke, F The Typhoid Carrier Problem Report of a Study of One Hundred and Ten Typhoid Carriers at the Manteno State Hospital, Manteno, Ill, *J A M A* **118** 964 (March 21) 1942

44 Cutting, W C, and Robson, G B The Alleged Efficiency of Medicinal Treatment of Typhoid Carriers, *J A M A* **118** 447 (April 25) 1942

45 Ames, W R Treatment of Typhoid Carriers, *J A M A* **119** 1217 (Aug 8) 1942

46 Levi, J E, and Willen, A The Typhoid Carrier State Treated with Sulfaguanidine, *J A M A* **116** 2258 (May 17) 1941

47 Hoagland, R J The Typhoid Carrier State Treated with Sulfaguanidine, *J A M A* **120** 1211 (Dec 12) 1942

48 Saphir, W, Baer, W H and Plotke, F Treatment of Typhoid Carriers with Iodophthalein, *J A M A* **119** 582 (June 13) 1942

## News and Comment

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**Meeting of American College of Chest Physicians Canceled**—At its midwinter meeting, held in Chicago on February 14, the Board of Regents of the American College of Chest Physicians voted to cancel the meeting of that association this year for the same reasons that the 1943 Annual Session of the American Medical Association has been canceled

The Board of Regents recommended that in those instances in which it is feasible state and district chapters of the college arrange to meet jointly with their state and district medical societies and assist in preparing scientific programs concerning the specialty of diseases of the chest

**Wartime Public Health Conferences**—The American Public Health Association will sponsor a three day Wartime Public Health Conference in New York, Oct 12 to 14, 1943

The program of the conference will be devoted exclusively to wartime emergency problems as they affect public health and the public health profession

influence of the initiating factor is extended to the common duct, then stones in the common duct, infection and cholangitis, biliary obstruction and hepatic cirrhosis may eventually develop

They classify diseases of the gallbladder into three main groups on the basis of the different etiologic factors concerned, as follows

- I Disorders resulting in disturbances of the filling and emptying mechanism of the gallbladder
  - A Anatomic causes (mechanical)
    - 1 External—congenital or acquired
      - (a) Adhesions—congenital or inflammatory
      - (b) Abnormal cystic artery
      - (c) Pancreatic inflammation—edema, fibrosis with involvement of the common duct
      - (d) Tumors of the pancreas and the extrahepatic bile ducts
    - 2 Internal—all congenital
      - (a) Convoluted cystic duct—valve of Heister obstruction
      - (b) Septums—phrygian cap
  - B Physiologic causes (functional)
    - 1 Hypertonic dyssynergia
    - 2 Hypotonic dyssynergia
- II Disorders resulting in disturbances of the concentrating function of the gallbladder
  - A Infectious cholecystitis
  - B Reflux of pancreatic juice
  - C Abnormal concentration of special elements
    - 1 Bile salts
    - 2 Calcium—calcified wall of the gallbladder
    - 3 Calcium carbonate—"milk of calcium" gallbladder
    - 4 Cholesterol—cholesterosis
- III Disorders in blood and metabolism resulting in disturbances of the gallbladder
  - A Hemolytic jaundice—congenital hemolytic icterus, sickle cell anemia, etc
  - B Cholesterol metabolism
    - 1 Pregnancy
    - 2 Obesity

They then discuss the effects of each of these factors in detail with regard to their relative frequency, the special symptom complex when present, the characteristic diagnostic findings by duodenal drainage and roentgen examination. The medical and surgical treatment is outlined, and the progressive course of the disease in the untreated patient is discussed. The presentation is concise. In the opinion of the reviewer, it is the most satisfactory presentation of this whole field of disease of the gallbladder and biliary tract to date.

To the present time there had not appeared an authoritative "small book useful chiefly to medical students and medical practitioners, in which these persons will find a resumé of the significant information upon the animal parasites of medical importance" This gap the author seeks to fill

The task is not an easy one, and Dr Culbertson is to be congratulated on having presented a useful textbook As was to be expected, in view of the author's special interests, the discussions of natural resistance, acquired immunity and immunologic procedures, though concise, are of particular value Tabulations of such material as "the route of infection, final site of residence and chief effects of the important parasites of man," diagnostic procedures and drugs used for treating infections with animal parasites will be particularly appreciated by students concerned with term examinations

There are numerous inaccuracies throughout the text, some of which are probably chargeable to proofreaders Manson's suggestion of the significance of mosquitoes as vectors of filariasis was first made in 1877, not 1879, *Glossina palpalis* was shown to transmit sleeping sickness in 1903, although the development in the fly was demonstrated in 1909, the British Plague Commission in India in 1906 presented conclusive evidence of the role of fleas in the spread of plague, and it was promptly put to practical test in this country in 1907 Ross did not begin his studies first "in the malaria of birds," but for the first three years worked on malaria in human beings On page 7 it is stated that "*Leishmania* were seen in 1900," but on page 90 one finds that "*Leishmania tropica* was probably first observed by Cunningham in 1885, but first accurately described by Borvosky, a Russian, in 1898" Since biopsy is looking at living tissue, one does not "decide to biopsy the spleen and look for *Leishmania*" (page 88)

In the discussion of the parasites themselves there are not a few statements which are open to question It is inaccurate to state regarding *Endamoeba histolytica* that in dogs only trophozoites are procured The author includes the mink as a host of *Paragonimus westermani* but does not mention the occurrence of lung flukes in North America It is doubtful whether *Cercaria elvae* is as widely concerned with schistosome dermatitis as is *Cercaria stagnicolae*, although the latter species is not mentioned In view of the careful experimental studies of Japanese investigators, it would seem overconservative to say regarding *Hymenolepis nana* that "it is not proved that man is infected from the rodent host or that rodents are infected from man" The discussion of Arthropoda of medical importance is especially sketchy, and the descriptions fall far short of giving enough morphologic information to "enable the student to identify and differentiate the organisms which are discussed"

Unfortunately, little aid in identification is afforded by the 140 photographs on 21 plates, distributed with little regard to the text which they are intended to illustrate For this the publisher's desire to keep down costs of reproduction is doubtless largely responsible

In spite of its deficiencies "Medical Parasitology" will be welcomed by many teachers and students on account of its concise, clearcut presentation of essential material relative to the important animal parasites of man

**Disease of the Liver, Gall-Bladder and Bile Ducts** By S S Lichtman, M D Price, \$11, buckram Pp 906, with 122 engravings and a colored plate Philadelphia Lea and Febiger, 1942

This book is a scholarly piece of work The author has reviewed the literature of a complicated subject in a workman-like fashion and from this and his own experience has created an excellent textbook

The early chapters deal with the most recent anatomic concept of the liver lobule The illustrations of this are particularly good Next is discussed the physiology of the liver, with appropriate attention to the relation to the biliary system of bilirubin, bile acids, bile salts and vitamins Then such topics as exogenous hepatic poisons and the role of nutrition and diet in the management of hepatic disease are considered The pathogenesis of jaundice and, in fact, of all pathologic conditions of the liver, is well described Considerable emphasis is given to the cirrhoses, though all disorders of the liver and its appendages receive appropriate consideration

The symptoms of disease of the biliary tract are discussed from the viewpoint of correlating as far as possible laboratory data with clinical experience This proves an interesting method of approach Another useful part of the book deals with a critical evaluation of the various tests now employable for estimating biliary function

The author is conservative and sound in his views His book promises to be popular with medical students and physicians Certainly it can be recommended

## Book Reviews

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**Biological Symposia Vol IX, Sex Hormones** Edited by F C Koch and P E Smith  
Price, \$2.50 Pp 146 Lancaster, Pa Jaques Cattell Press, 1942

Volume IX is part of a series devoted to current symposiums in the field of biology. It contains four papers on the actions and metabolism of sex hormones, and four papers on hormonal factors in the inversion of sex.

Prof Carl Moore, of the University of Chicago, presented the biologic introduction to the symposium on sex hormones. No one is better qualified to do this. It is his opinion that the testes and ovaries can be regarded as the principal, although not the exclusive, source of androgens and estrogens. These hormonal substances carry the principal responsibility for inducing the functional maturity of the male and the female complex, including the structural portions of the reproductive system, as well as the psychic or behavioral reactions. A specific genetic constitution to some extent different in the two sexes provides the background or framework on which the hormones operate. It has been abundantly demonstrated that the hormones exhibit considerable capacity to modify the normal expression of the opposite genetic constitution.

Dr A T Kenyon, assistant professor of medicine, University of Chicago, wrote the next paper, entitled "The Comparative Metabolic Influences of the Testicular and Ovarian Hormones in Man." He expresses the belief that the androgens exert anabolic effects on tissues other than those of the genital system. He mentions growth in weight and height of the human body after injections of androgens. A rise in production of heat and retention of nitrogen also occur and with this, retention of the associates of nitrogen in protein formation.

Estradiol benzoate also induces reduction in urinary nitrogen, but the dose known to be effective is so large that it is not clear whether this effect is a physiologic manifestation of ovarian function.

The third paper is by Prof E A Doisy on "The Metabolism of the Estrogens." He reviews the anabolism and catabolism of these hormones. In large measure because of the investigations of Doisy himself sufficient data, apparently based on substantial grounds, are now at hand to establish the sources of estrogens and the means by which their destruction is effected.

Prof F C Koch treats androgens in a similar manner. His article contains several especially interesting paragraphs on changes in excretion of sex hormones in disease, including tumors of the adrenal glands and Addison's disease.

The bibliographies of both Doisy's and Koch's paper are lengthy, and no doubt contain the best papers relative to the biochemistry of estrogens and androgens.

Of the group of papers concerned with hormonal factors in the inversion of sex, the one by Dr R R Greene on "The Effects of Sex Hormones on Embryonic Sexual Structures of the Rat" is outstanding. This work represents the combined efforts of Dr M W Burrill, Dr A C Ivy and the author in the departments of physiology, pharmacology and gynecology of Northwestern University Medical School. Their work seems to establish the fact that sex hormones can markedly modify the differentiation of the sexual structures in the rat embryo.

To obtain such effects, large amounts of the hormonal substance concerned must be administered to the pregnant rat. If the dose is sufficient, the substance is apparently able to traverse the maternal circulation, reach the embryo and modify its sexual development.

These papers on sex inversion contain experimental data and theories that apply primarily to the animals studied. Such work, however, is necessarily pertinent to any consideration of similar conditions in human beings. As is stated by one of the authors, the factors influencing the normal tendencies of the genotype are numerous and varied, but among them the hormones are of outstanding importance. In so far as it is possible in these short papers the authors evidence a critical and broad approach to the subject at hand. To interested persons this book is well worth careful reading and study.

**Medical Parasitology** By James T Culbertson, College of Physicians and Surgeons  
Price, \$4.25 Pp 285, with 16 text figures and 21 plates New York Columbia University Press, 1942

Recent years have seen the appearance of several American textbooks on animal parasitology, and this year they were augmented by Strong's comprehensive revision and enlargement of Stitt's textbook on tropical diseases and by Belding's book on clinical parasitology.

## PERIPHERAL VASCULAR RESPONSE TO ACUTE ANOXIA

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AND

HARRY LANDT, M D

AND

JULIEN E BENJAMIN, M D

CINCINNATI

The more general reactions of the cardiovascular system of man to the inhalation of oxygen-poor gas mixtures have been described by numerous investigators<sup>1</sup>. They consist of an almost immediate increase in the heart rate, a slight rise in the systolic blood pressure, with no significant change in the diastolic level, and a definite augmentation in the cardiac output. With respect to alterations in the peripheral circulation, the results are not as clearcut. Freeman and his associates<sup>2</sup> studied the rate at which blood flows through the hand during a period of acute anoxia, using the venous occlusion plethysmographic method. They found that either an increase or a decrease of rate was produced. Gellhorn and Steck,<sup>3</sup> utilizing the same procedure and the same vascular bed, also noted apparently inconsistent results, the flow being decreased, unchanged or slightly increased.

Since the circulation through the hand is affected by a variety of vasoconstricting stimuli,<sup>4</sup> it was considered worth while in the present study to investigate the effect of acute anoxia on the flow of blood through the forearm and the leg, as well. Changes noted in these vascular beds are for the most part not complicated by vasomotor effects.

From the May Institute for Medical Research, Jewish Hospital

This work was aided by a grant from the Samuel and Regina Kuhn Fund

A preliminary report was published elsewhere (Abramson, D I, Landt, H, and Benjamin, J E. Peripheral Vascular Response to General Anoxia, *Proc Soc Exper Biol & Med* **48** 214, 1941)

1 Schneider, E C, and Truesdell, D. The Circulatory Responses of Man to Anoxemia, *Am J Physiol* **71** 90 (Dec) 1924. Gellhorn, E, and Lambert, E. The Vasomotor System in Anoxia and Asphyxia, Urbana, Ill, University of Illinois Press, 1939. Graybiel, A, Missiuro, V, Dill, D B, and Edwards, H T. Experimentally Induced Asphyxiation in Cardiac Patients, with Especial Reference to Certain Hazards in Air Travel and to the Use of Asphyxiation as a Cardiac Functional Test, *J Aviation Med* **8** 178 (Dec) 1937.

2 Freeman, N E, Shaw, J L, and Snyder, J C. Peripheral Blood Flow in Surgical Shock. Reduction in Circulation Through the Hand Resulting from Pain, Fear, Cold and Asphyxia, with Quantitative Measurements of the Volume Flow of Blood in Clinical Cases of Surgical Shock, *J Clin Investigation* **15** 651 (Nov) 1936.

3 Gellhorn, E, and Steck, I E. Effect of the Inhalation of Gases with a Low Oxygen and Increased Carbon Dioxide Tension on the Peripheral Blood Flow in Man, *Am J Physiol* **124** 735 (Dec) 1938.

4 Capps, R B. Method for Measuring Tone and Reflex Constriction of Capillaries, Venules and Veins of the Human Hand with Results in Normal and Diseased States, *J Clin Investigation* **15** 229 (March) 1936. Abramson, D I, and Ferris, E B, Jr. Responses of Blood Vessels in the Resting Hand and Forearm to Various Stimuli, *Am Heart J* **19** 541 (May) 1940.

**The Antigonadotropic Factor, with Consideration of the Antihormone Problem**  
By Bernhard Zondek and Felix Sulman Price, \$3 Pp 185 Baltimore Williams & Wilkins Co, 1942

In this monograph Zondek and Sulman present a rather full discussion of the problem of the antigonadotropic problem. They not only include a review of the literature but describe a few unpublished observations of their own. The data are divided and discussed as follows: "Historical Review," "The Antihormone Theory of Collip," "The Antigonadotropic Factor," "Clinical Significance of the 'Antihormones'" and "Mechanism of the Antigonadotropic Reaction." The authors present evidence which they believe strongly indicates that the antigonadotropic substances are to be classified "as a group of immune bodies of a character hitherto unknown in serology."

The monograph should be of great interest not only to persons interested in endocrinology, but to physiologists, biochemists, immunologists and internists. It tends to emphasize the immunologic mechanisms of antigonadotropic activity instead of the point of view that an antagonistic hormone is secreted that neutralizes gonadotropic substances. Many aspects of this problem, obviously, will remain unanswered until the gonadotropic hormones and their "antagonists" are isolated in a chemically pure state.

**Familial Nonreaginic Food-Allergy** By Arthur F. Coca Price, \$5 Pp 160 Springfield, Ill. Charles C. Thomas, Publisher, 1943

Coca believes he has been able to delimit a group of cases of food allergy which differs in several respects from atopic ("reaginic") allergy. Allergic reagins or antibodies are not demonstrable by direct or indirect cutaneous testing, the hereditary influence controlling the occurrence of this type of allergy is independent of the atopic inheritance, many of the symptoms are not represented in the atopic group, and the allergic reaction practically always causes acceleration of the pulse. The symptoms of patients with such allergy are of extremely wide scope, ranging from physical fatigue to heartburn. Thus, their conditions comprise a wider range of ailments than is customarily accepted as being allergic in origin. Coca considers it possible in most instances to determine by means of the pulse rate all offending foods and other excitants with a high degree of accuracy. The method consists of establishing the basal pulse rate and its daily range. An increase of rate in excess of 14 beats a minute is thought to be diagnostic of antigenicity. This book will undoubtedly be considered provoking. The results of these studies will have to be repeated before these newer concepts and methods will be generally accepted.

**Psychotherapy in Medical Practice** By Maurice Levine, M.D. Price, \$3.50 Pp 320 New York The Macmillan Company, 1942

The past few years have seen an increasing interest in psychosomatic medicine. This has led to the production of several new books each composed with the worthy object of making understandable to the general reader the essentials of modern psychiatry and psychotherapy.

It is a difficult matter for any author to write simply about any phase of how the mind works. Thus, certain attempts in this line have seemed to sacrifice completeness for the sake of simplicity or, on the other hand, have been too abstruse for the average physician or medical student.

Here is a useful compromise. The author has put together a practical book which is interestingly written so as to be readable and authoritatively written so as to be informative. It describes well the difficulties to be overcome in successful estimation of the effect of emotional disturbances on human relations and outlines the various methods of psychotherapy now available. It gives a well chosen list of references to current literature. On the whole, it is worth having in one's library.

**Religion and Health** By Seward Hiltner Price, \$2.50 Pp 292 New York The Macmillan Co, 1943

This is not a quack book but a thoughtful scholarly treatise by a serious student of the relation of religion to health. Granted that physicians now recognize the importance of physical and mental health, Dr. Hiltner would lay an additional emphasis on spiritual well-being and its place in the armamentarium of healing. While the point of view is developed against the background of Christian philosophy, the treatment is a broad one which goes to the roots of what spiritual aid can accomplish in helping a sick person. Young physicians especially, who perhaps have felt that physics and chemistry are enough to solve the problem of disease, would profit much from a careful reading of this book.

of breathing through a mask, in some cases, despite definite attempts to counteract it, this feeling persisted during the rest of the experimental period. The actual application of the mask resulted in a further decrease of blood flow in the hand in 1 subject and a slight increase in 2 others. After the subjects began breathing the oxygen-poor gas mixture, variable results were obtained. In 3 there was a definite progressive decrease in blood flow coincident with the onset of the period of anoxia (chart 1) and in 5 a slight decrease or no change, while in 2 a significant increase was noted. In both of the latter (B P and R B) the control flow was initially rather low. With readmission of atmospheric air to the system, the circulation remained depressed for at least the following fifteen minutes in 2 subjects, slowly rose in 1, while in 7 it rapidly increased to reach a level considerably higher than

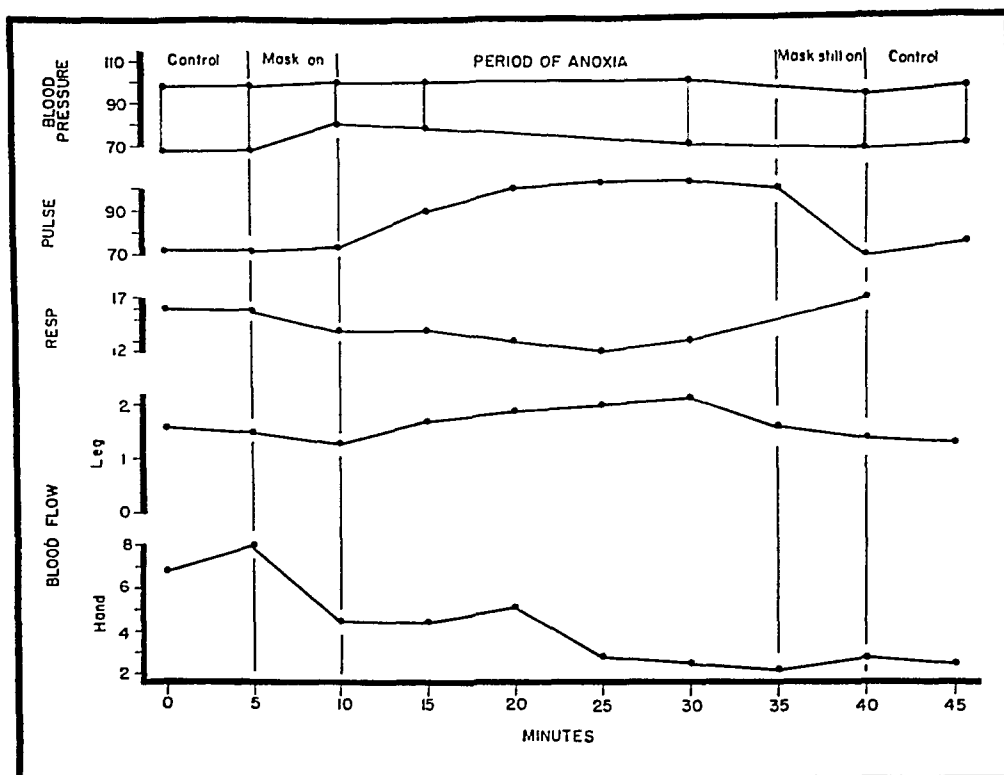


Chart 1—Effect of relative anoxia on the rate at which blood flowed through the hand and the leg, with the simultaneous effects on the respiratory and pulse rates and the blood pressure

the control flow. In 2 of the latter group the blood flow then fell after a short interval, while in the remaining 5 it continued elevated for the rest of the experimental period.

*Forearm*—The vascular responses in the forearm were studied in 10 subjects (table 2, chart 2). The figures for the blood flow at rest were for the most part within the lower range of the average of 1.8 cc per minute per hundred cubic centimeters of limb volume ( $\sigma$ , 0.7) for the control series. On application of the mask there was a significant increase in the blood flow in 2 subjects and little change in the others. With the onset of the period of anoxia, the rate of blood flow remained practically unchanged during at least the first five minutes, and then there was a small but definite progressive increase in 6 of the subjects (chart 2), while in 4 no change or even a slight decrease was observed. Two of the latter subjects were rather apprehensive, and previously it had been demonstrated that there was a significant augmentation in blood flow in the forearm merely with the application of the mask (J B and M L). On readmission of room air there was an almost



## METHOD

The work was performed on a series of 25 subjects with normal cardiovascular systems. By means of the venous occlusion plethysmographic method, the blood flow in cubic centimeters per minute per hundred cubic centimeters of limb volume was determined separately in the hand, the forearm and the leg, generally two of these sites were studied simultaneously, according to the technique previously described.<sup>5</sup>

The temperature of the water in the plethysmograph was maintained at 32 C, and the room temperature between 25 and 27 C. In order to determine whether the subjects when at rest had blood flow readings which fell within the range of normal, the results obtained in a group of 90 persons previously reported on<sup>6</sup> were utilized as controls.

In each instance the subject inhaled a constant mixture of oxygen and nitrogen in which the concentration of the former gas ranged between 10.5 and 94 per cent in the different experiments. The gas mixture was obtained from a spirometer and an auxiliary reservoir and the exhaled air was automatically discharged into the room through an outlet tube and flutter valve. Special precautions were taken to minimize the dead space in the apparatus and to use a mask which fitted close to the face, so that there was little chance for loss of gas mixture or for introduction of room air into the system.

The usual procedure consisted of taking 15 readings of blood flow after the subject had become accommodated to the environment and was at rest and then applying the mask to the face. A similar number of determinations was made while the subject breathed room air through the mask. Following this, the connection between the mask and the spirometer was opened without the subject's being aware of the change, and a third set of readings was obtained at intervals of one minute during the entire period of relative anoxia, this period lasted from ten to twenty-seven minutes in the different experiments. At the end of it the patient was permitted to breathe room air again, and then, after all readings had returned to normal, the mask was removed from the face, a set of determinations was made in each of these periods. Besides readings of blood flow, the blood pressure, the pulse rate and the respiratory rate were recorded at short intervals during the experiment.

In a number of cases the circulatory response to a period of work was determined, first while the subject breathed room air and then in the middle of the period of anoxia. In each instance this was accomplished in the following manner. A series of readings of blood flow were made with the subject resting, after which the forearm in the plethysmograph was exercised by means of ipsilateral manual compression of a blood pressure bulb connected to an air-filled 5 gallon (19 liter) bottle. The pressure in the system was raised to 30 mm of mercury by compressing the bulb twenty-five to thirty times in a period of one-half minute. Immediately after the termination of the exercise, readings of blood flow were taken at short intervals (every ten or fifteen seconds) until the flow appeared to return to the previous control level. From these determinations a graph was constructed, and by means of a planimeter the quantity of blood over and beyond the amount which would ordinarily have entered the forearm at rest was obtained.<sup>7</sup> The figure was expressed as cubic centimeters of blood flow repayment per hundred cubic centimeters of limb volume. With this quantity of work, the circulatory response generally lasted no longer than eight minutes. As a result the exercise could be performed at the end of ten minutes of inhalation of the oxygen-poor gas, at a time when the state of anoxia was fully developed, and still sufficient time would be present for full recovery from the work to take place before the twenty to twenty-five minute period of anoxia was terminated.

## RESULTS

*Hand*—The vascular responses in the hand were studied in 10 subjects (table 1, chart 1). The control blood flow readings, taken while the patient was at rest, were for the most part smaller than the average of 9.3 cc per minute per hundred cubic centimeters of limb volume ( $\sigma$ , 2.1),<sup>8</sup> obtained in another group of normal subjects. This may have been due to the apprehension caused by the anticipation

5 Abramson, D. I., Zazeela, H., and Marrus, J. Plethysmographic Studies on Peripheral Blood Flow in Man. I. Criteria for Obtaining Accurate Plethysmographic Data, *Am Heart J* **17** 194 (Feb.) 1939. Ferris, E. B., Jr., and Abramson, D. I. Description of a New Plethysmograph, *ibid* **19** 233 (Feb.) 1940.

6 Abramson, D. I., and Fierst, S. M. Resting Blood Flow and Peripheral Vascular Responses in Hypertensive Subjects, *Am Heart J* **23** 84 (Jan.) 1942.

7 Abramson, D. I., and Fierst, S. M. The Peripheral Vascular Response to Exercise in the Hyperthyroid State, *J Clin Investigation* **20** 517 (Sept.) 1941.

8 The alpha signifies standard deviation.

immediate decrease in blood flow in those subjects who had shown an increase, with a return to the control level in five to ten minutes

*Leg*—The vascular responses in the leg were studied in 15 subjects (table 3, charts 1 and 3) The control readings all fell within the range of 1.4 cc per minute

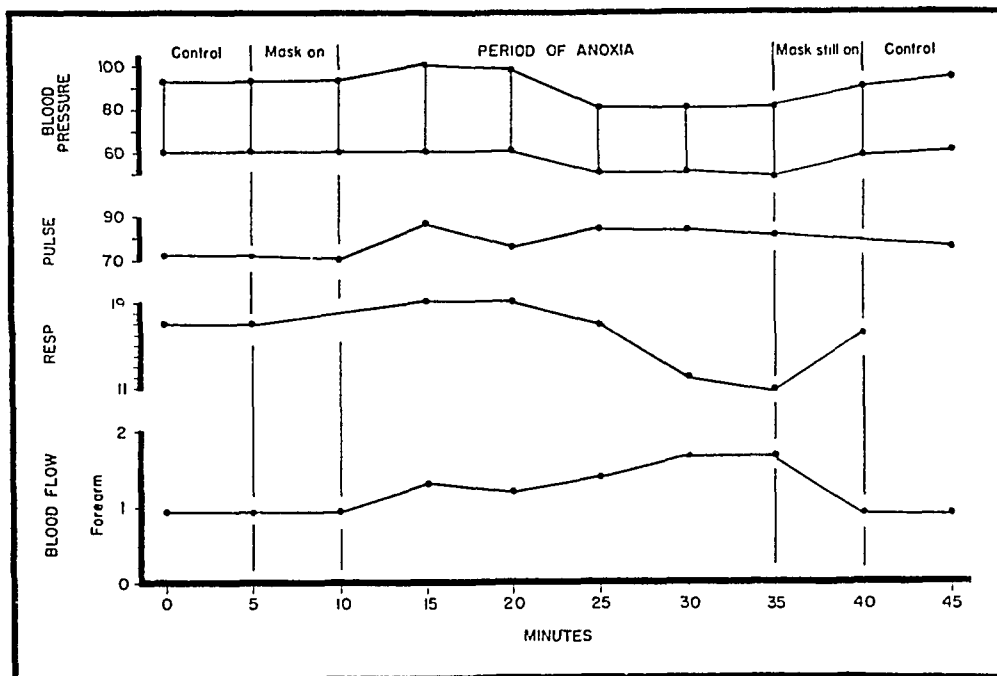


Chart 2—Effect of relative anoxia on the rate at which blood flowed through the forearm, with the simultaneous effects on the respiratory and pulse rates and the blood pressure

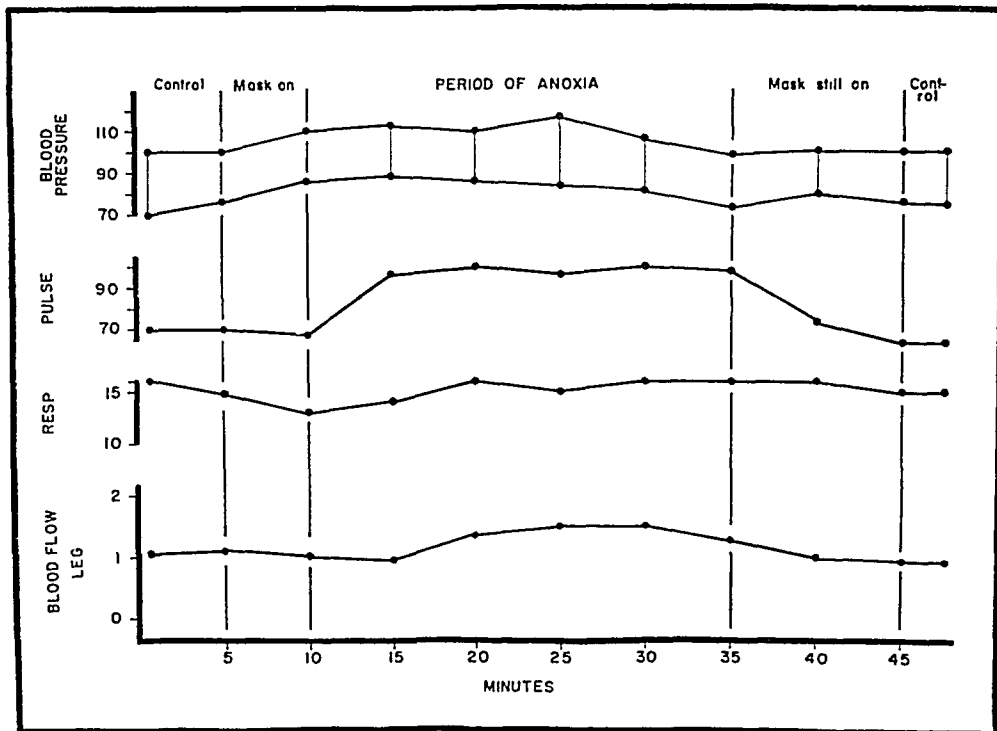


Chart 3—Effect of relative anoxia on the rate at which blood flowed through the leg, with the simultaneous effects on the respiratory and pulse rates and the blood pressure

per hundred cubic centimeters of limb volume ( $\sigma$ , 0.5) for normal subjects. On application of the mask, no significant change took place in the rate of blood flow except in 1 person (M F), who was apprehensive and in whom an increase was noted with this procedure. In the first five minutes of the period of anoxia no definite alteration in circulation was observed in any of the subjects (chart 3)

TABLE 1—*Peripheral Vascular Changes in the Hand During a Period of Anoxia*

Subject	Percent O <sub>2</sub>	Dura- tion of Anoxia, Min	Blood Flow, Cc per Min per 100 Cc of Limb Vol				Pulse Rate per Min				Blood Pressure				
			Con- trol	Mask On	Anoxia	Mask On	Con- trol	Mask On	Anoxia	Mask On	Con- trol	Mask On	Anoxia	Con- trol	Mask On
J S	10.1	20	2.7	1.1	5 min 3.2 10 min 4.0 15 min 3.8 20 min 4.7	6.1 6.1 6.1 6.1	5.6 5.6 5.6 5.6	77	76	5 min 104 10 min 126 15 min 112 20 min 100	80 71 71 76	96/70	98/70	96/68	98/70
H K	10.3	27	4.3	5.1	5 min 3.4 10 min 4.3 15 min 4.8 20 min 4.7 25 min 4.7	1.2 1.2 1.2 1.2 1.2		61	67	5 min 72 10 min 86 15 min 90 20 min 108 25 min 106	91	93/66	98/70	112/70 106/68	101/66
B P	10.3	25	2.5	2.0	5 min 2.6 10 min 3.3 15 min 3.3 20 min 6.1 25 min 6.1	5.5 6.1 6.1 6.1 6.1	5.7 4.9 4.8	70	68	5 min 96 10 min 80 15 min 100 20 min 96 25 min 100	71 64 64 64	100/71	100/76 100/80	100/76 100/80	100/76
R B	10.1	20	2.3	2.8	5 min 2.8 10 min 4.2 15 min 4.7 20 min 5.0	5.6 9.1 9.1 9.1	4.7 6.6	102	102	5 min 120 10 min 110 15 min 123 20 min 126	96 96 86 90				
A M	10.0	22	7.7	1.5	5 min 1.1 10 min 5.1 15 min 2.8 20 min 2.5	2.1 2.7 2.7 2.5	2.1	71	71	5 min 81 10 min 90 15 min 102 20 min 100	91 70 72	95/66	100/40 100/78 100/70	91/66	100/70 95/70
J L	10.0	20	5.6	5.1	5 min 3.4 20 min 1.6	1.7 1.6	4.6	75	80	5 min 100 10 min 100 20 min 115	100 81				
D M	10.2	20	1.5	1.6	5 min 3.2 20 min 4.1	6.6 4.1	3.2	65	68	5 min 75 10 min 90 20 min 110	90 75 60				
I C	10.0	10	2.8	2.8	5 min 1.6 10 min 1.6	2.0 1.9		76	68	5 min 91 10 min 99	63 65	102/75	100/75 100/78	106/40	101/78
V S	9.7	10	7.8	7.8	5 min 0.9 10 min 5.8	11.2 5.8		71	75	5 min 91 10 min 96	81 76	112/75	120/71 122/78	120/72 116/71	108/72 110/71
C V	10.0	10		8.6	5 min 6.1 10 min 6.1	9.6 9.0	10.0								

TABLE 3—Peripheral Vascular Changes in the Leg During a Period of Anovula

Subject	Percent age O <sub>2</sub>	Dura- tion of Anovula, Min	Blood Flow, Cc per Min per 100 Cc of Limb Vol				Pulse Rate per Min				Blood Pressure			
			Con		Mask		Con		Mask		Con		Mask	
			trol	On	Anovula	On	trol	On	Anovula	On	trol	On	Anovula	On
J H	10.2	20	1.0	1.2	5 min 1.2 10 min 1.4 15 min 1.4 20 min 1.4	1.0	1.1	73	5 min 82 10 min 88 15 min 86	58 62	112/68	116/82	5 min 116/76 15 min 114/78	101/72 110/72
H S	9.8	20	1.2	1.1	5 min 1.1 10 min 1.2 15 min 1.3 20 min 1.4	1.2	1.1	84	5 min 90 10 min 102 15 min 118 20 min 112	86	106/72	110/72	5 min 106/76 10 min 108/72 15 min 106/72	106/66 106/76
M A	10.0	20	1.4	1.1	5 min 1.3 10 min 1.3 15 min 1.5 20 min 1.6	1.1	1.5	72	5 min 84 10 min 100 15 min 100 20 min 100	68	118/72	122/72	5 min 122/72 10 min 124/72 15 min 126/70 20 min 124/70	
L N	9.4	15	1.1	1.4	5 min 1.5 10 min 1.7 15 min 2.0	1.7 1.6	1.3 1.4	81	5 min 108 10 min 102 15 min 92	84 76	112/68	114/70	5 min 116/70 10 min 112/70 15 min 114/68	108/68 108/68
J K	10.5	15	1.3	1.6	5 min 1.4 10 min 1.3 15 min 1.4	1.2		76	5 min 84 10 min 90 15 min 86	69 69	104/70	108/72	5 min 110/70 10 min 108/70 15 min 108/70	108/62
M F	10.1	20	1.3	2.0	5 min 2.4 10 min 1.9 15 min 2.1 20 min 2.1	1.6 1.3 1.4	1.3 1.0	86	5 min 122 10 min 116 15 min 124 20 min 114	105 82 88	120/74	130/82	5 min 130/90 10 min 125/84 15 min 120/74 20 min 114/70	110/80 110/80
G L	10.2	20	1.7	1.8	5 min 2.1 10 min 2.1 15 min 2.6 20 min 2.0	2.0 1.6	1.5 1.3	80	5 min 92 10 min 94 15 min 98 20 min 92	72 78	118/74	118/80	5 min 120/84 10 min 120/84 15 min 118/80 20 min 118/78	118/84 120/80
J S *	10.1	20	1.1	1.4	5 min 1.3 10 min 1.8 15 min 1.8 20 min 1.5	1.3 1.2 1.3	1.1							
C V *	10.0	10.0	1.2	1.2	5 min 1.5 10 min 1.6 15 min 2.3 20 min 2.2	1.7 1.0	1.0							
V S *	9.7	10.0		2.0	5 min 2.3 10 min 2.2 15 min 2.1 20 min 2.9	2.0 1.7								
I C *	10.0	10.0		0.9	5 min 1.0 10 min 1.3 15 min 1.5 20 min 2.2 25 min 2.4	1.0 0.9	1.5 1.7							
R B *	10.1	20.0	1.5	1.5	5 min 1.5 10 min 2.2 15 min 2.1 20 min 2.9	1.9 2.0	1.5 1.7							
B P *	10.3	25	1.1	1.0	5 min 0.9 10 min 1.3 15 min 1.4 20 min 1.5 25 min 1.2	1.0 0.9	0.9 1.3 1.3							
H K *	10.3	27	0.7	1.0	5 min 1.0 10 min 1.1 15 min 1.1 20 min 0.8 25 min 1.0	1.0	0.9							
A M *	10.0	22	1.6	1.3	5 min 1.7 10 min 1.9 15 min 2.0 20 min 2.1	1.6 1.4	1.3							

\* The changes in pulse rate and blood pressure recorded for these subjects are included in table 1

TABLE 2—*Peripheral Vascular Changes in the Forearm During a Period of Anoxia*

Subject	Percent O <sub>2</sub>	Duration of Anoxia, Min	Blood Flow, Cc per Min per 100 Cc of Limb Vol				Pulse Rate per Min				Blood Pressure			
			Mask On	Anoxia	Mask On	Con trol	Mask On	Anoxia	Mask On	Con trol	Mask On	Anoxia	Mask On	Con trol
J D	10.1	20	1.0	5 min 1.1 10 min 1.1 15 min 1.3 20 min 1.4	1.1 1.0	1.0	86	5 min 106 10 min 110 15 min 106 20 min 98	88	96/74	96/74	5 min 104/76 10 min 104/72 15 min 104/74 20 min 94/61	98/76	96/72
F II	10.1	25	0.9	5 min 1.3 10 min 1.2 15 min 1.4 20 min 1.7 25 min 1.7	1.3 1.3 1.0	1.3	72	5 min 87 10 min 92 15 min 84 20 min 84 25 min 82	75	91/64	92/60	5 min 100/60 10 min 94/50 15 min 80/50 20 min 80/50 25 min 80/48	90/58 88/58	94/60 92/60
C W	10.4	25	0.6	5 min 0.6 10 min 0.6 15 min 0.6 20 min 0.9 25 min 0.9	0.8 0.5 0.6	0.5	71	5 min 92 10 min 104 15 min 108 20 min 112 25 min 106	78	96/46	100/50	5 min 106/46 10 min 104/40 15 min 108/40 20 min 96/46 25 min 98/44	100/48 96/50	96/52 102/54
R B	10.1	20	0.9	5 min 0.8 10 min 0.8 15 min 1.0 20 min 0.8	0.7 0.8 0.6	0.7	76	5 min 105 10 min 104 15 min 106	96	101/58	106/58	5 min 112/62 10 min 110/64 15 min 112/60	112/62 108/60	106/58 102/58
J B	10.1	25	1.8	5 min 2.0 10 min 1.8 15 min 1.6 20 min 2.1 25 min 2.2	2.1 1.6	2.0	80	5 min 118 10 min 126 15 min 120 20 min 124 25 min 126	126	110/76	118/80	5 min 126/84 10 min 126/80 15 min 120/82 20 min 120/72 25 min 118/78	118/84	116/78
S II	10.2	25	1.1	5 min 1.3 10 min 1.1 15 min 1.1 20 min 1.1 25 min 1.2	1.1 1.2	1.0	78	5 min 87 10 min 87 15 min 81 20 min 82 25 min 80	82	130/78	118/80	5 min 120/80 10 min 116/78 15 min 120/80 20 min 116/80	120/78 116/78	116/80 116/80
M L	10.1	15	1.7	5 min 2.7 15 min 2.7	2.4	1.8	96	5 min 97 10 min 110 15 min 107	85	130/76	130/72	5 min 130/72 10 min 128/60	130/72 132/80	136/70
K F	10.1	20	2.7	5 min 3.3 20 min 3.0	2.7	2.6	75	5 min 88 10 min 90 15 min 90	68	71				
J L*	10.0	20	1.0	5 min 0.9 20 min 1.3	1.0 0.9	1.1								
D M*	10.2	20	1.4	5 min 1.4 20 min 2.0	1.6 1.1	1.1								

\* The changes in pulse rate recorded for these subjects are included in table 1

observation of Freeman and his co-workers that there is a uniform increase in flow through the sympathectomized hand under these circumstances suggests that the different types of reactions normally elicited are in some way related to the presence of vasoconstrictor nervous impulses. According to Gellhorn and Steck, the variability in the results is due to the fact that the increased vasoconstrictor tonus resulting from the stimulation of the vasomotor center competes with the local dilatory effect of the different metabolites formed in the presence of oxygen deficiency, the rate of blood flow being determined by which of the two factors predominates. We also feel, however, that the element of apprehension associated with the procedure, even in the case of trained subjects, plays an important role in this respect. Another possibility which may contribute to the vasoconstriction in this site is the increase in the depth of respiration frequently noted in the latter portion of the anoxic state, for a deep breath by itself has been shown to produce a marked decrease in blood flow through the fingers<sup>10</sup>. Because of all these complicating factors, the responses of the vessels in the hand to a lack of oxygen cannot be considered to be representative of peripheral blood flow and hence should not be given much significance as far as general responses are concerned.

With respect to the results in the forearm and the leg, it can be stated that in the majority of the cases a small but definite and progressive increase in peripheral blood flow was observed during the period of relative anoxia. Of interest in this respect are the findings of Grollman,<sup>11</sup> who investigated the circulatory effect of a series of oxygen and nitrogen mixtures. He noted that no change in cardiac output took place until the oxygen had fallen to 11.6 per cent, when the concentration dropped below this point, the readings for the minute volume output rose rapidly. These findings have since been confirmed by a number of investigators.<sup>12</sup> It is quite possible, therefore, that since approximately a 10 per cent oxygen mixture was used in the present study, the increase in blood flow in the forearm and the leg resulted in part, at least, from an augmented cardiac output elicited by the lack of oxygen. Further, the alteration in circulation may also have been due to the local vasodilatory effect of want of oxygen on the vessels themselves. A complicating consideration is the fact that under the influence of anoxia the respiratory minute volume increases and consequently carbon dioxide will be blown off in greater than normal amounts, this in turn resulting in a state of acapnia. It is possible that under such circumstances there might be a decrease in venous return to the heart due to a reduction in the tonus of striated muscle as well as in the tone of the vasomotor center, this would eventually manifest itself in the form of diminished peripheral circulation. However, since the opposite response was observed, it can be inferred either that this factor did not play an important role in altering the blood flow under the present experimental conditions or that the increased cardiac output elicited by the anoxia more than compensated for any decrease that might have resulted from the acapnia alone.

The finding that the pulse rate increased almost at once while the changes in blood flow were first noted five to ten minutes after the onset of anoxia suggests

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10 Mulinos, M. G., and Shulman, I. The Effects of Cigarette Smoking and Deep Breathing on the Peripheral Vascular System Studied by Five Methods, *Am J M Sc* **199** 708 (May) 1940.

11 Grollman, A. Physiological Variations of Cardiac Output in Man. The Effect of High Altitude on Cardiac Output and Its Related Functions, Account of Experiments Conducted on Summit of Pike's Peak, Colorado, *Am J Physiol* **93** 19 (May) 1930.

12 (a) Asmussen, E., and Chiodi, H. The Effect of Hypoxemia on Ventilation and Circulation in Man, *Am J Physiol* **132** 426 (March) 1941. (b) Wiggers, C. J. Cardiac Adaptations in Acute Progressive Anoxia, *Ann Int Med* **14** 1237 (Jan) 1941.

Then, in 11, the rate of blood flow began to increase, and the augmented circulation was maintained during the remainder of the period, with readmission of room air into the system, the flow quickly returned to the previous control level (charts 1 and 3). In 4 of the subjects, no real alteration in circulation through the leg was noted during or after the anoxic period. These findings to some extent are similar to those of Lennox and Gibbs,<sup>9</sup> who studied changes in arteriovenous oxygen differences in blood from the leg following inhalation of oxygen-poor gases. They found that pronounced anoxia resulted in an increased flow in this vascular bed while with a milder form a decrease was noted, the latter observation being difficult to explain, according to these investigators.

With respect to the other determinations it was found that in every instance the pulse rate began to rise almost immediately after the onset of the period of anoxia (charts 1, 2 and 3), the maximal average acceleration for the group being 27 beats per minute. As soon as this period was terminated the pulse rate quickly fell, in some instances temporarily reaching a lower level than that observed at the beginning of the experiment. The effect on blood pressure was much less marked (charts 1, 2 and 3). In 5 instances no change in the systolic level took place, while in the remaining 16 cases there was an average rise of 6 mm of mercury. The

TABLE 4—*Peripheral Vascular Response to Exercise During Anoxia\**

Subject	Control Period				Period of Anoxia			
	Total Blood Flow Repayment,† Cc	Maximal Single Response Cc per Min per 100 Cc of Limb Vol	Time of Maximal Response Sec	Duration of Recovery Period Min	Total Blood Flow Repayment, Cc	Maximal Single Response Cc per Min per 100 Cc of Limb Vol	Time of Maximal Response, Sec	Duration of Recovery Period, Min
J. L.	10.1	7.3	15	8	15.7	7.1	25	9
K. F.	12.2	8.2	20	6	13.5	9.7	20	6.5
D. M.	16.9	9.1	20	7.5	19.6	13.5	0	9.0

\* The pressure in a 5 gallon bottle was raised to 70 mm of mercury in each instance by the subject's compressing a blood pressure bulb twenty seven to thirty times in approximately one half minute.

† This means the excess quantity of blood for each 100 cc of limb volume entering the extremity during the period of recovery.

diastolic level, for the most part varied insignificantly. The respiratory rate either increased or decreased somewhat (charts 1, 2 and 3), the respiratory movements generally being of somewhat greater amplitude in the latter part of the anoxic period. Except for occasional complaints of light-headedness and headache and some cyanosis of the face and hands, the subjects experienced no untoward effects from the inhalation of the oxygen-poor gas mixture.

*Circulatory Response to Exercise*—In the 3 subjects in whom the response to a definite quantity of exercise in the anoxic state was studied, the blood flow repayment was either somewhat or definitely greater than that obtained in the control period (table 4). Further, the first few readings obtained immediately after the exercise was terminated revealed that the blood flow generally rose to a higher level than was observed during the control period. The period of recovery was also a little longer.

#### COMMENT

It is obvious that the response of the blood vessels of the hand to acute general anoxia is variable, our findings in this respect being similar to those of Freeman and his associates<sup>2</sup> and of Gellhorn and Steck.<sup>3</sup> In contrast, the

9 Lennox, W. G., and Gibbs, E. L. Blood Flow in the Brain and the Leg of Man, and the Changes Induced by Alteration of Blood Gases, *J. Clin. Investigation* **11** 1155 (Nov.) 1932.

Associated with the increase in the blood circulating through the forearm and the leg were a significant augmentation in pulse rate, a slight elevation of systolic blood pressure and variable changes in the rate of respiration

The circulatory response to a period of exercise during the inhalation of the oxygen-poor gas was compared with that obtained under normal circumstances. The results were interpreted to indicate that the compensatory adjustments to work in a state of relative anoxia were not as adequate as those elicited normally.

The possible mechanisms responsible for the circulatory changes present during a period of anoxia are discussed.

Dr Kamillo Flachs and Dr Sidney M Fierst cooperated in this study, and Miss Robert Senior and Mrs William Littleford gave valuable technical assistance.

19 Garfield Place



that there was no causal relation between these two factors. Further, it does not seem as though the alteration in pulse rate was dependent on want of oxygen in the tissues, since it appeared much before this state could have been reached. The change can more likely be explained on the basis of central stimulation resulting in increased accelerator nerve activity and decreased vagal tone<sup>12,13</sup>. Finally, the observation of Schmidt and Comroe<sup>13</sup> that in animals low oxygen tension produces acceleration of pulse only in the presence of intact chemoreceptors of the carotid body may also apply to this condition in man.

The fact that a greater than 50 per cent decrease in oxygen content (from 20.9 per cent in air to 10 per cent in the mixture) produced only a moderate change in peripheral blood flow is readily understandable if one considers that in the normal subject under resting conditions only a small proportion of the total quantity of oxygen in the arterial blood is removed in passage through the vessels of muscles. It would be expected, therefore, that during anoxia of the degree utilized in the present study there would be no necessity for a marked increase in the rate of peripheral blood flow in order to satisfy the oxygen requirements of the resting tissues.

The findings with exercise are in accord with the aforementioned view. As previously reported,<sup>7</sup> the magnitude of the postexercise blood flow repayment is an indication of the efficiency of the compensatory mechanisms elicited during the period of work and also of the metabolism of the tissues involved. In other words, the performance of a specific amount of work requires the expenditure of a certain amount of energy, the latter being restored through the nutritive materials in the blood stream. In order to effect this, there is a local increase in the blood flowing through the tissues both during the actual work and in the postexercise period. On the basis that the metabolism of the tissues does not change significantly during a short period of relative anoxia, our findings with exercise assume some significance. The fact that a greater postexercise blood flow repayment was elicited in the case of the work performed under want of oxygen indicates that the compensatory mechanisms functioning during the exercise were not as adequate as under normal conditions, and hence a greater portion of the blood flow debt had to be repaid subsequently. Since one of the adjustments called forth by exercise is an increase in the utilization of arterial oxygen, it can readily be seen that during want of oxygen the quantity of this gas obtained in this manner might not be as great as under ordinary conditions. Therefore, the increased amount of oxygen required during work would have to be satisfied by a greater than normal augmentation in the rate of peripheral blood flow.

#### SUMMARY AND CONCLUSION

The effect on the peripheral circulation of a period of relative anoxia was studied in a series of 25 normal subjects by the venous occlusion plethysmographic method. The inhalation of an oxygen-poor gas mixture (approximately 10 per cent oxygen and 90 per cent nitrogen) for periods of from ten to twenty-seven minutes produced a small but definite increase in the rate at which blood flowed through the forearm and the leg in the majority of subjects and generally a decrease in the circulation in the hand. In view of the fact that the vessels in the hand respond to all types of vasoconstricting stimuli, the results obtained during the period of anoxia were not given much general significance.

13 Schmidt, C. F., and Comroe, J. H., Jr. Functions of Carotid and Aortic Bodies, *Physiol. Rev.* 20: 115 (Jan.) 1940.

## MATERIAL STUDIED

The coronary arteries of 135 selected hearts were carefully studied. Ninety per cent of the patients had been more than 40 years of age at the time of death. Standard procedures of examination were carried out. In addition, a special method of treating arteries which were suspected of being involved by recently occluding lesions was employed. These arteries were dissected intact from the hearts, fixed, dehydrated in alcohol and finally cleared in pure benzene as a preliminary step to the cutting of segments for embedding in paraffin. This procedure facilitated the location of proper sites for sectioning without distortion of the tissue, which is rendered friable by hemorrhagic lesions. Intimal hemorrhage was observed in 54 of the 135 cases (40 per cent). The hemorrhagic lesions<sup>6</sup> ranged from 2 or 3 mm in diameter to massive processes which extended several centimeters along the course of an artery and caused collapse of the intima and resultant obliteration of the lumen.

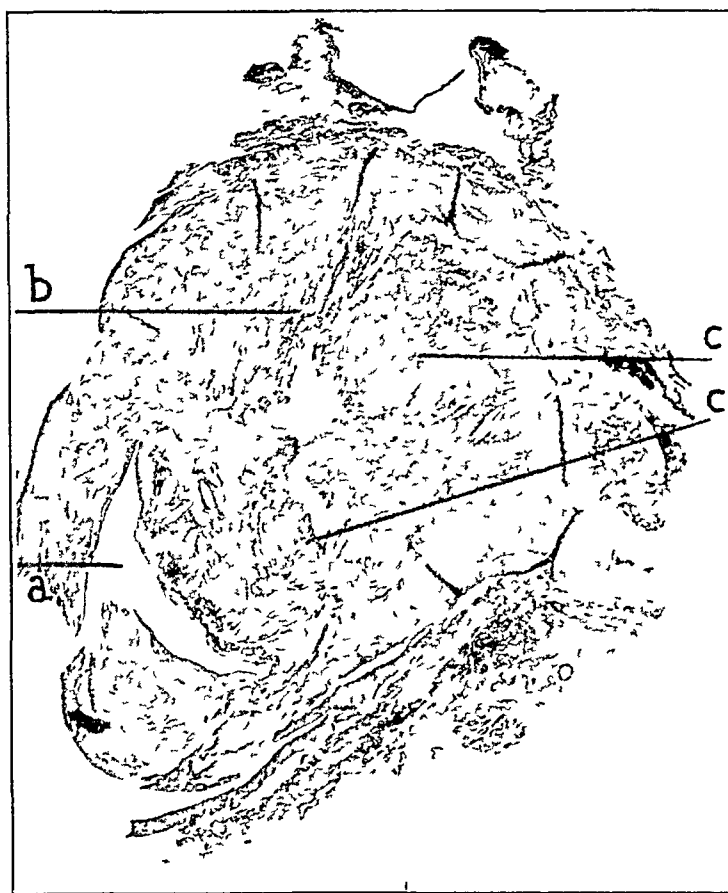


Fig 1—The lumen, *a*, of this coronary artery has been almost obliterated by an intimal process which consists of large lipoid-containing cells, elements of organization and hemorrhage. Many young capillaries are present among the lipoid-containing cells, *b*, and there are a few scattered lymphocytes. Hemorrhage, *c*, is relatively minimal. There was no coronary thrombus, although the patient died during a severe attack of angina pectoris. Changes indicative of recent myocardial infarction were not observed ( $\times 14$ ).

Among the individual arteries examined were 20 in which recent occlusion was found, and in at least 9 of these the occlusion had been directly produced by hemorrhagic arterial lesions. Similar lesions were present in the other 11 occluded arteries, but associated arterial thrombi were considered the direct cause of occlusion. Many organized hemorrhagic lesions were observed, particularly in arteries in cases in which healed or chronic myocardial infarcts were found. That these lesions had contained extravasated blood was determined by the presence of phagocytosed iron pigment.

<sup>6</sup> The term "hemorrhagic lesion" is used in preference to "intimal hemorrhage" to avoid the assumption that hemorrhage is the cause of arterial occlusion.

# HEMORRHAGIC LESIONS OF THE CORONARY ARTERIES

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Several types of acute occlusion of the coronary arteries have been described.<sup>1</sup> Interpretation of the pathologic changes associated with the more familiar form, usually accompanied by arterial thrombosis, has not resulted in a clear understanding of the basic factors involved. In recent years more emphasis has been accorded to the hemorrhage in the intimal and subintimal layers of the occluded arteries and several authors have attached great importance to this phenomenon in the mechanism of coronary occlusion. This has resulted partly from a relatively new interpretation of the origin and significance of hemorrhage in the walls of small arteries. It had generally been considered that extravasated blood in this location either was derived from the lumen of the artery or occurred as a result of inflammatory exudation.<sup>2</sup> Lately it has been demonstrated that in most instances intramural hemorrhage of the coronary artery arises from the vascular channels of the intima, these being especially numerous in the neighborhood of atheromatous plaques.<sup>3</sup> According to the recent theories, which deal with the relation of subintimal hemorrhages to acute occlusion of the coronary artery, bleeding from these tiny channels causes arterial occlusion either directly by pressure of the resulting hematoma<sup>2d</sup> or indirectly by precipitation of a thrombus near the site of the hemorrhage. Among the factors acting to produce such hemorrhages, it has been proposed that fluctuations in blood pressure play an important part.<sup>2c</sup>

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1 (a) Benson, R. L. The Present Status of Coronary Arterial Disease, *Arch. Path.* **2** 876-916 (Dec.) 1926. (b) Faulkner, J. M., Marble, H. C., and White, P. D. The Differential Diagnosis of Coronary Occlusion and of Cholelithiasis, *J. A. M. A.* **83** 2080-2082 (Dec. 27) 1924. (c) Hamman, L. The Symptoms of Coronary Occlusion, *Bull. Johns Hopkins Hosp.* **38** 273-319 (April) 1926.

2 (a) Paterson, J. C. Vascularization and Hemorrhage of the Intima of Arteriosclerotic Coronary Arteries, *Arch. Path.* **22** 313-324 (Sept.) 1936, (b) Capillary Rupture with Intimal Hemorrhage as a Causative Factor in Coronary Thrombosis, *ibid.* **25** 474-487 (April) 1938, (c) Some Factors in the Causation of Intimal Haemorrhages and in the Precipitation of Coronary Thrombi, *Canad. M. A. J.* **44** 114-120 (Feb.) 1941. (d) Waitman, W. B. Occlusion of the Coronary Arteries by Hemorrhage into Their Walls, *Am. Heart J.* **15** 459-470 (April) 1938. (e) Horn, H., and Finkelstein, L. E. Arteriosclerosis of the Coronary Arteries and the Mechanism of Their Occlusion, *ibid.* **19** 655-682 (June) 1940.

3 Winternitz, M. C., Thomas, R. M., and LeCompte, P. M. Studies in the Pathology of Vascular Disease, *Am. Heart J.* **14** 399-404 (Oct.) 1937. Nelson, M. G. Intimal Coronary Artery Haemorrhage as a Factor in the Causation of Coronary Occlusion, *J. Path. & Bact.* **53** 105-116 (July) 1941. Paterson (footnote 2a, b and c).

4 (a) Leary, T. Vascularization of Atherosclerotic Lesions, *Am. Heart J.* **16** 549-554 (Nov.) 1938. (b) Boyd, A. N. An Inflammatory Basis for Coronary Thrombosis, *Am. J. Path.* **4** 159-166 (March) 1928. Benson<sup>1a</sup>.

5 Leary, T. Atherosclerosis. Special Consideration of Aortic Lesions, *Arch. Path.* **21** 419-458 (April) 1936. Paterson (footnote 2a, b and c). Horn and Finkelstein<sup>2e</sup>. Leary<sup>4a</sup>.

elements as large lipophages or their granular remnants, lymphocytes, fibroblasts chains of endothelial cells and hemorrhage in various stages of dissolution and absorption. Cholesterol crystals were not so prevalent in these as in older lesions. Essentially the same picture was to be found at other levels of an involved artery, in varying



Fig. 3—Two levels of a coronary artery illustrating the relationship of a thrombus to a hemorrhagic arterial lesion. Upper. The section was made near the head of the thrombus, *a*, which was originally adherent to the arterial wall and overlay the intimal change, *b*. Lower. At the lower level the intimal change is more advanced.

degrees of advancement, sometimes with little, if any accompanying hemorrhage. At no point did the quantity of extravasated blood seem commensurate with the size of the lesion as a whole. In fact, a few large occluding lesions were observed

## MICROSCOPIC FEATURES OF HEMORRHAGIC ARTERIAL LESIONS

Wherever hemorrhage was encountered in the intima of a coronary artery, coexistent degenerative changes were to be found which in most cases denoted an active pathologic process. The involved portion of intima was thickened, and

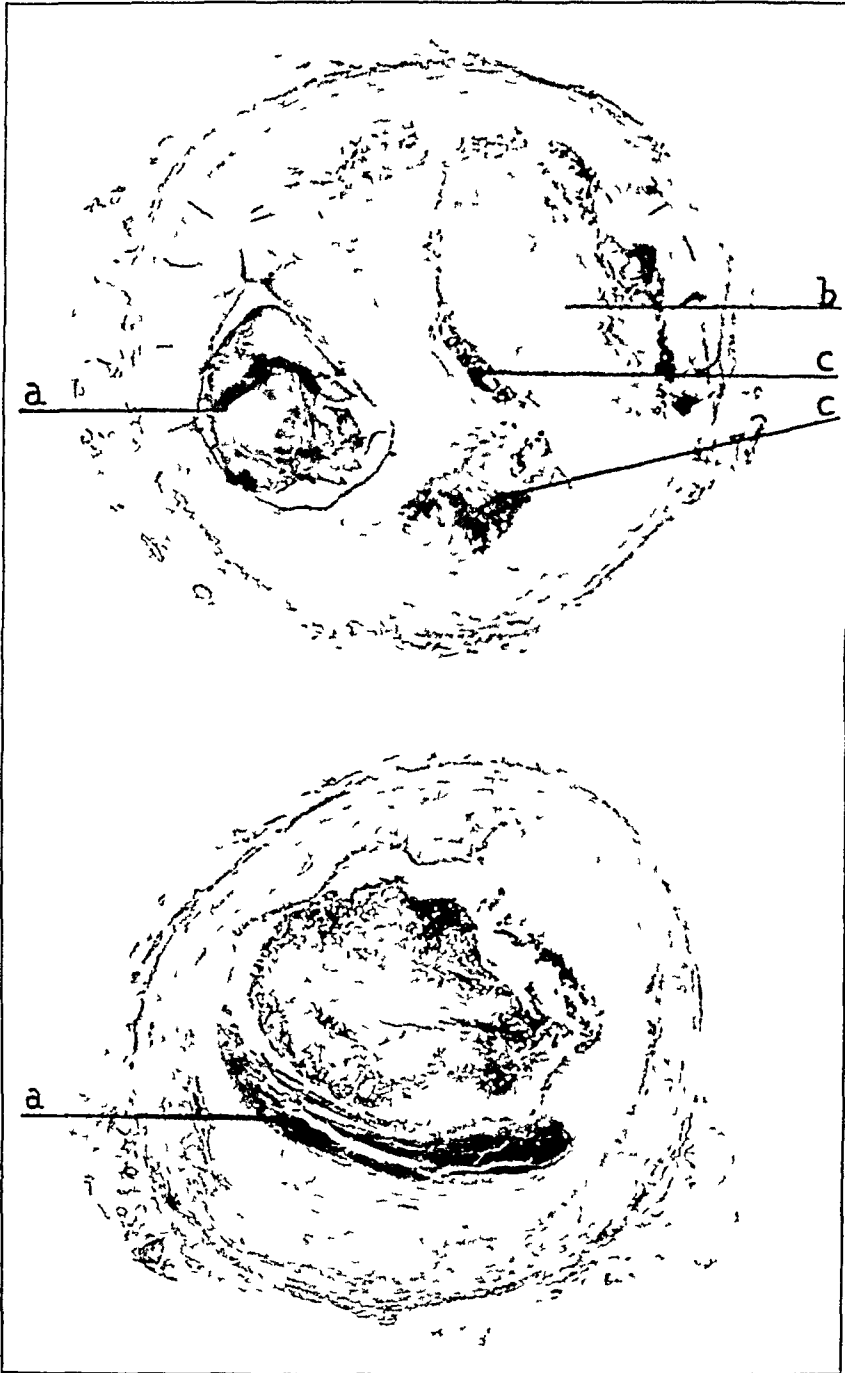


Fig 2—Upper and lower. Two levels of a coronary artery involved throughout almost its entire course by a hemorrhagic process. The lumen, *a*, which was obliterated at some levels, was filled with either a late antemortem or a postmortem thrombus. Most cellular elements had been destroyed, but large blotches of lipid substance, *b*, probably represent residua of lipid-containing cells. In isolated areas the lesion is stained with hemorrhage, *c*.

the planes of tissue were separated, distorted and generally displaced toward the lumen of the artery. The interstices of the intimal connective tissue contained such

Lesions of the first group (figs 1, 2 and 3) were encountered most frequently, attained the greatest size and were the pathologic finding in all but 2 of the 9 instances in which acute coronary occlusion had been produced directly by hemorrhagic arterial lesions. The largest lesions extended along the greater portion of the artery, replaced its lumen and in consistency and gross appearance somewhat



Fig 5—An unusual type of hemorrhagic lesion. Upper. Gross appearance of the hemorrhagic lesion, *a*, as brought out by a clearing method. Lower. Microscopic appearance, the lesion, *b*, consisted of hemorrhage, lymphocytes, endothelial cells, phagocytosed as blood pigment and young capillaries. The reduced lumen, *c*, partially obstructed by a mural thrombus, *d*, may be noted. The heart in this case was involved by an acute myocardial infarct.

resembled recent thrombi. Sections of these lesions were observed microscopically to consist principally of large lipid-containing cells or their granular remnants. The latter, which were composed of lipid globules, frequently retained the general

which, although accompanied by a relatively small amount of hemorrhage, were nevertheless the only apparent cause of acute myocardial infarction in some cases or of sudden death during attacks of angina pectoris in others. Such lesions retained their cellular configuration more completely, but were altered by varying degrees of early organization.

It did not seem logical from any standpoint to assume that hemorrhage was the primary factor in the production of these occluding lesions. Any expanding intimal process, whatever its nature, of necessity develops a pressure equal to or greater than that of the blood within the arterial lumen. The pressure of blood within the coronary arteries in all probability surpasses that within microscopic intimal blood channels, even though some or all of them should arise from the arterial lumen itself. It also seems probable that the quantity of extravasated blood in the lesions observed was a measure of the number of capillaries and vascular spaces disrupted by the primary pathologic condition, their contents diffusing into neighboring portions of the intima but not bleeding actively into it.

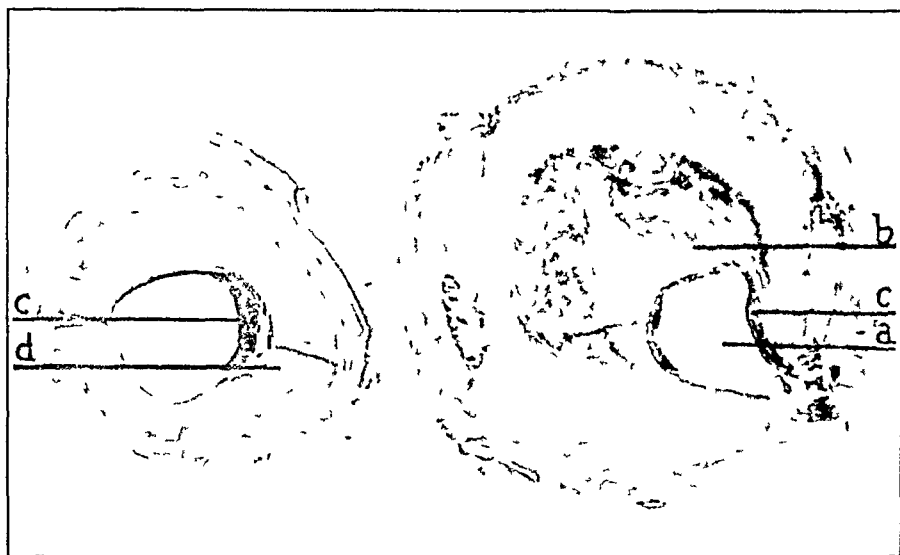


Fig. 4—The lumen, *a*, of this coronary artery was displaced and obliterated (at a lower level) by a hemorrhagic intimal process, *b*, consisting of fibrillar intimal change, hemorrhage, elements of organization and lymphocytic proliferation. Mural thrombosis is present in the main artery as well as in its adjacent branch, *c*. In the latter, *d*, however, the intimal change has not become hemorrhagic, although in other respects it was similar. The pathologic change began well away from the lumen, separated from it by normal intimal tissue. An acute myocardial infarct resulted from this lesion.

Arterial thrombi when present were invariably associated with hemorrhagic lesions. In each instance of an arterial thrombus, examination of the arterial wall along its course revealed the type of intimal change that has been described accompanied by hemorrhage. Mural thrombi were usually attached to the endothelial surface overlying these lesions, and it was noted with interest that they overlay the lesions in their entirety and were not confined to areas of hemorrhage, this finding further substantiates the conception that hemorrhage in itself is not the most significant factor in the pathologic condition represented.

The three general groups of recent hemorrhagic arterial lesions encountered were (1) those in which hemorrhage was related to the presence of numerous lipoid-containing cells, (2) those characterized by hemorrhage in association with proliferative intimal changes and (3) those in which small hemorrhages were adjacent to calcified plaques.

intermingled with extravasated blood in the intimal stroma, although considerable variation was present in the proportion of cell types among the different lesions. Arterial thrombosis also was frequently related to lesions of this type.

The third group of lesions (fig 6) was characterized by small localized hemorrhages, usually adjacent to calcified plaques. These lesions were not associated with acute arterial occlusion or thrombi and were seldom recognized grossly. Lipoid-containing cells were absent, and the degree of organization was variable. The relationship between these lesions and the calcium deposits was not clear. The process was apparently one of low grade activity and resulted in dense, calcified lesions. In general, this type of lesion was present among the older patients.

#### COMMENT

The grouping of these lesions is general because it was not possible to divide them into clea-cut types. An attempt has not been made to interpret the significance of the wide variation in the pathologic pictures among the lesions, except to consider it as representing grades of activity. This may be true to only a limited extent. Wherever intimal hemorrhage occurred, however, there appeared to be ample basis for it in the accompanying pathologic picture, and the elements which composed that picture were interpreted as being responsible not only for the hemorrhage but also for the associated occluding phenomenon and any coexistent thrombi.

#### SUMMARY AND CONCLUSIONS

Hemorrhagic lesions were observed in the walls of the coronary arteries in 54 of 135 hearts (40 per cent) and were directly or indirectly related to acute occlusion of the coronary artery in 20. The lesions were characterized by hemorrhage associated with the presence of large lipoid-containing cells, proliferative intimal changes and organization. Smaller, less active lesions usually were found adjacent to calcified plaques. The intimal changes that coexisted with the hemorrhage appeared to represent the primary factor in the pathologic condition, the hemorrhage was secondary. It does not seem logical, moreover, that hemorrhage in itself can have produced the effects observed.

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outline of the cells. Extravasated blood was invariably present. If the compressed arterial lumen was not obliterated, it either remained patent or was obstructed by a thrombus.

A few of the lesions of this group in which cellular configuration was only slightly altered were considered as representing less active processes. In these such organization as was present was early and minimal and much of it was



Fig 6—Upper and lower. Small hemorrhages, *a*, that were commonly seen in relation to calcareous plaques and were not associated with acutely occluding lesions.

far enough removed from hemorrhage to be considered independent of it. Chains of endothelial cells extended among the lipid-containing cells, and lymphocytes, fibroblasts and other wandering cells were present.

The second group of lesions (figs 4 and 5), in which hemorrhage was associated with more conspicuous proliferative changes, appeared to represent a lower grade of activity than the first group. The large lipid-containing cells were absent. Lymphocytes, young capillaries, fibroblasts and endothelial cells were

quently over a two year period, with good response. During the year prior to admission the patient had again become dyspneic and edematous. Edema of the face had appeared four to five days before admission, when the swelling of his legs was so marked that fluid began to ooze. Inquiry revealed that his diet over several years had consisted of polished rice, white bread and Chinese vegetables, with occasional fish and pork, and had rarely included fruit.

*Physical Examination*—On admission the rectal temperature was 36.6 C (97.9 F), the pulse rate 60 per minute, respirations 20 per minute and the blood pressure 126 systolic and 80 diastolic measured in millimeters of mercury. There were slight cyanosis of the lips and nail beds, massive anasarca and marked exertional dyspnea but no orthopnea. The skin of the entire body was dry and scaling. Over the distal portion of the extremities there were irregular macular patches of brownish discoloration with marked thickening and lichenification. There was fissuring of the skin at the commissures of the mouth and over the bridge and at the lateral angles of the nose. About the external nares were small, reddened areas of ulceration. Marked edema of the eyelids was present, the conjunctivas were engorged and discharged thick purulent material. The sides of the tongue were smooth and reddened. Over the lower lobe of the right lung there was slight dullness, and a few crepitant rales were audible at the base of each lung. The apical impulse of the heart was diffuse and was located in the left midaxillary line. On percussion the heart was enlarged both to the right and to the left. The cardiac sounds were distant and the rhythm totally irregular, and a soft systolic murmur was heard at the apex. The peripheral pulses were synchronous and equal, the vessels pliant. There was moderate venous engorgement with the edge of the liver palpable 7 cm below the costal margin, and there was evidence of ascites. The spleen was not palpable. There was partial phimosis, and thick, greenish, purulent material covered the glans penis. Edema of the legs was marked, with fluid oozing through superficial cutaneous ulcerations. There was also edema of the arms and forearms. On neurologic examination there were generalized hyperesthesia to pinprick and tenderness of the calves and soles of the feet, and the ankle jerks were absent. Vibration and position senses were preserved, and the plantar responses were flexor.

*Laboratory Data*—Urinalysis revealed a positive reaction for albuminuria (3 plus) but no sugar, cells or casts. Examination of the blood revealed 15 Gm of hemoglobin per hundred cubic centimeters, 5,800,000 red cells, 9,600 leukocytes, a normal smear and differential count, a negative serologic reaction for syphilis (Kline test), 5.9 mg of serum proteins per hundred cubic centimeters, 21 mg of urea nitrogen per hundred cubic centimeters, an icteric index of 17 and 140 mg of serum cholesterol per hundred cubic centimeters. Gonococci were not found in cultures of the urethral discharge. Gastric secretion contained 70 degrees of free hydrochloric acid after stimulation with histamine. Intravenous administration of 1,000 mg of ascorbic acid yielded only 31 mg in the urine during the test period. The vital capacity was 1,100 cc.

An electrocardiogram showed marked right axis deviation. Auricular fibrillation was present, with occasional ventricular premature contractions. The form of the T waves and the RT segments suggested myocardial damage but may have been due in part to recent administration of digitalis. Circulation time measured by sodium dehydrocholate was twenty-one seconds, and venous pressure was 210 mm of solution of sodium chloride on direct measurement. A teleroentgenogram (fig 1) showed a small amount of fluid at the base of the left lung but gave no suggestion of parenchymal disease. The heart was enlarged in all diameters.

*Course of Illness*—Ten milligrams of thiamine hydrochloride was given intravenously for three days, in addition to the daily oral dose of 60 mg. The parenteral dose was then increased to 50 mg for eighteen days after which interval it was discontinued. During this regimen there was no change in symptoms, physical signs or the electrocardiographic pattern. Nicotinic acid was then employed, and the cutaneous lesions improved slightly, but at this time the ventricular rate increased to 104 per minute and the patient appeared more acutely ill. After the intramuscular administration of 5 cc of a 10 per cent solution of digitan the apical rate decreased to 30 per minute. A diet high in vitamins supplemented with parenteral administration of vitamin preparations was begun. In addition, ammonium chloride and mercupurin were administered, and prompt diuresis resulted. Over a ten day period the body weight decreased from 64 to 54 Kg, with loss of edema. When the heart rate again became rapid, digitalis was given by mouth and the ventricular rate was maintained at 70 per minute by suitable doses. Auricular fibrillation persisted. The cutaneous lesions improved gradually, and the ulcerations on the legs healed. During the last month of life brewers' yeast was given in daily doses varying from 18 to 24 Gm, in addition to an oral dose of 30 to 60 mg of thiamine hydrochloride. On the fifty-third day of hospitalization the temperature rose sharply to 39 C.

# FIBROSIS OF THE ENDOCARDIUM AND THE MYOCARDIUM WITH MURAL THROMBOSIS

NOTES ON ITS RELATION TO ISOLATED (FIEDLER'S) MYOCARDITIS  
AND TO BERIBERI HEART

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AND

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Cardiac failure in young persons lacking the usual features of organic heart disease or associated renal lesions has frequently been ascribed to isolated (Fiedler's) myocarditis. A study of the reported cases of isolated myocarditis indicates a heterogeneous disease group related to known and to unknown infectious or toxic agents. Some changes are frankly inflammatory, others degenerative, some are acute, others subacute or chronic. Within the past few years evidence has accumulated that dietary deficiency can cause clinically evident heart disease which hitherto may have fallen into this vaguely defined classification. With advancing knowledge it becomes desirable to dissociate this group into more sharply defined types.

Recently we encountered 3 cases in which the patients died in the hospital of congestive failure of obscure origin. In all cases the patients were carefully studied during life and examined post mortem. Clinically and pathologically these cases resemble each other closely, and without recourse to the clinical history the anatomic diagnosis might well have been isolated myocarditis. Review of the history, clinical course and histologic data, however, suggests the possibility that the changes might have been due to long-continued dietary deficiency or defect in the absorption or utilization of certain accessory food factors. Similar lesions including marked cardiac hypertrophy and mural thrombosis, have been ascribed to beriberi heart by Dock<sup>1</sup>. They differ from those of acute beriberi heart adequately described by Wenckebach<sup>2</sup> and by Weiss and Wilkins<sup>3</sup>.

## REPORT OF THREE CASES

CASE 1—*History*—B. M., a 40 year old Chinese man, was admitted to New York Hospital on March 22, 1941. In 1933 the patient had lost 60 pounds (27 Kg) in weight over a three month period. A roentgenogram revealed an enlarged heart and was suggestive of pulmonary congestion. The blood pressure was 110 systolic and 80 diastolic measured in millimeters of mercury. After restricted use of meat and salt the patient's weight decreased further to 135 pounds (61 Kg). In 1936 edema of the ankles and nonproductive cough had appeared. Administration of a proprietary preparation of strophanthus and squill caused edema to disappear and relieved the cough. He had remained fairly well during the subsequent three years. When edema reappeared, mersalyl-theophylline solution was given fre-

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1 Dock, W. Marked Cardiac Hypertrophy and Mural Thrombosis in the Ventricles in Beriberi Heart, *Tr. A. Am. Physicians* 55:61, 1940.

2 Wenckebach, K. F. (a) *Das Beri-beri Herz*, Berlin, Julius Springer, 1934, (b) *The Riddle of the Beriberi Heart*, in *Contributions to the Medical Sciences in Honor of Dr. Emanuel Libman*, New York, International Press, 1932, vol. 3, p. 1198.

3 Weiss, S., and Wilkins, R. W. The Nature of the Cardiovascular Disturbances in the Nutritional Deficiency States (Beriberi), *Ann. Int. Med.* 11:104, 1937.

few monocytes and an occasional eosinophil were identified (fig 2D). The lungs were congested and edematous. In the lower lobe of the right lung a small infarct was undergoing organization. There was a thrombosed artery, and in the surrounding area were collections of large mononuclear cells containing golden yellow pigment. Similar cells were also encountered in smaller number in the alveolar spaces. The capillaries of the alveolar septums were engorged. Chronic passive congestion was also evident in the liver and the pancreas with slight increase in fibrous tissue in these organs. The spleen, kidneys and gastrointestinal tract also revealed passive congestion. A section of skin taken from the area of crsipelas

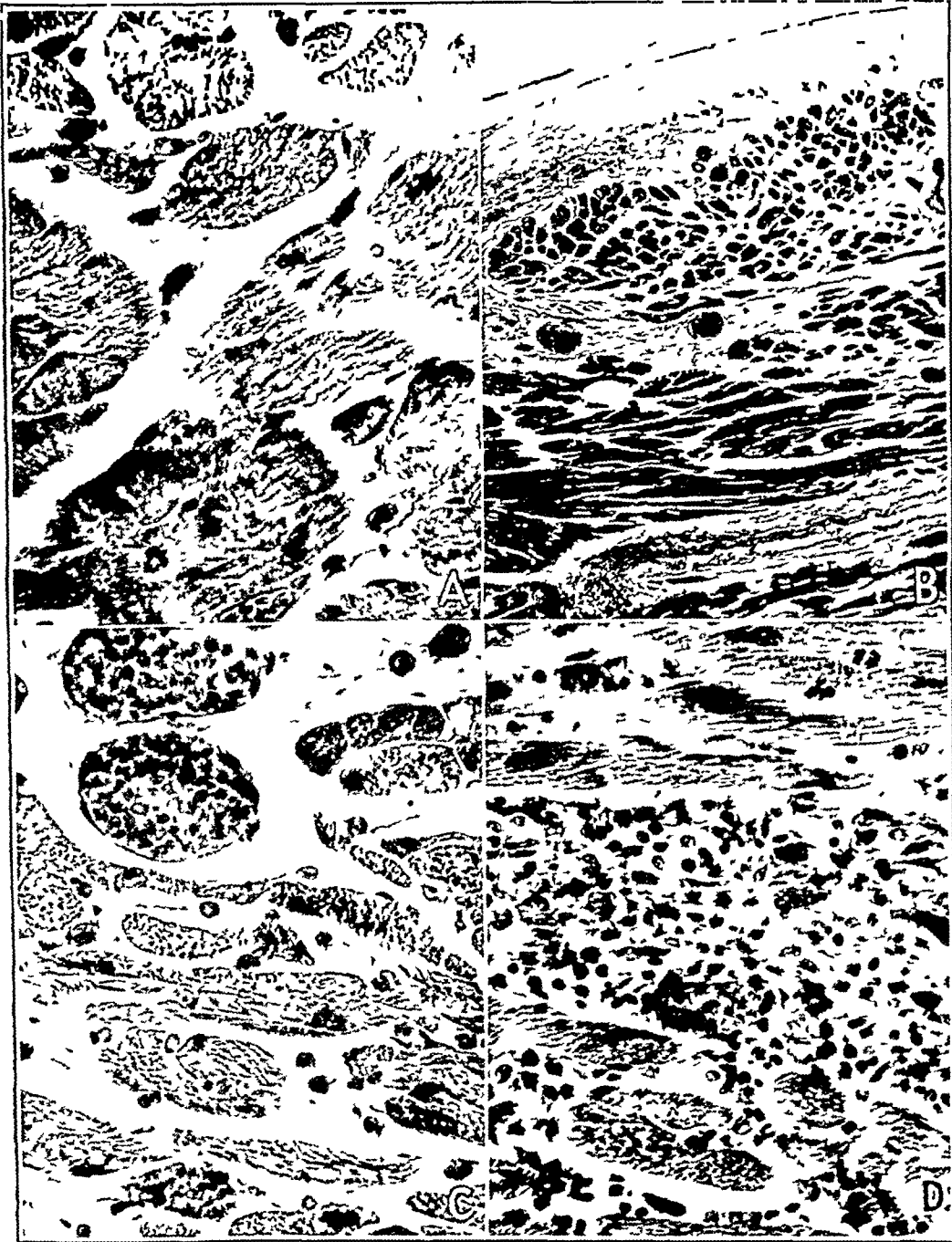


Fig 2 (case 1)—Several sections of the myocardium. Part A illustrates the “moth-eaten” appearance of the muscle fibers and the engorgement of the smallest vessels (*venose Stauung* of Wenckebach). Part D illustrates a small focus of cellular infiltration.

showed diffuse suppurative inflammation of the corium with large numbers of polymorphonuclear leukocytes in microscopic abscesses. Sections from deeply pigmented areas of the skin showed thickening of the epidermis with hyperkeratinization. The papillae were irregular. There was an increase in the number of melanin-containing cells, and the pigment was also seen in large amounts in the squamous plates, a change regarded by Moore and Spies<sup>4</sup> as characteristic of pellagra.

4 Moore, R. A., and Spies, T. D. Personal communication to the authors.

(1022 F) A red, swollen, sharply circumscribed area, typical of erysipelas, appeared on the face. The patient died suddenly the same day, May 12.

*Necropsy*—Gross Examination The right and the left pleural cavity contained 150 cc and 100 cc, respectively, of clear straw-colored fluid and the peritoneal cavity contained 600 cc. The heart weighed 650 Gm, the chambers of both the right and the left ventricle being greatly distended, their walls measured 5 mm and 10 mm, respectively. The myocardium of both ventricles was soft and red brown. On cut section congestion of the myocardial vessels was conspicuous. The endocardium of the left ventricle was thickened and contained one large area measuring 3 by 1 cm in which the increase in fibrous connective tissue measured 1 mm in thickness. Similar but smaller gray-white elevated patches were present in other places. A dry, friable thrombus was loosely attached to the pectinate muscles of the anterior and apical parts of the left ventricle. The right ventricle, especially the conus arteriosus, was markedly distended. In this chamber there were a few patchy areas of fibrous thickening of the endocardium similar to those seen in the left ventricle. The right auricle was moderately dilated.



Fig 1 (case 1)—A teleoroentgenogram taken three days after admission, showing a heart shadow enlarged both to the right and to the left, reaching the left lateral wall of the chest at the eighth rib posteriorly. This shadow obscures the lower portion of the left pulmonary field, but in addition there is increased density at the left costophrenic angle. A kymogram was abnormal only in flattening of the waves at the apex of the heart. This roentgenogram, as were all others reproduced here, was made at a 2 meter distance.

and a mural thrombus measuring 8 by 6 cm in its greatest diameters adhered firmly to the auricular appendage. The left auricle and the valve leaflets were not altered.

*Microscopic Examination* Sections of the myocardium showed a fine vacuolization of the muscle fibers in focal areas (fig 2A and C). There were only a few small areas in which the change similar to that designated by Wenckebach<sup>2</sup> as hydropic degeneration was noted. There was marked increase in fibrous connective tissue, and wide bands of connective tissue separated the muscle bundles in many places (fig 2B). In other areas there was merely slight interstitial edema. The smaller vessels, including capillaries of the myocardium, were engorged (fig 2C). The fibrous thickening of the endocardium observed in the gross specimen was striking in the sections (figs 2B and 3). Occasional islands of lymphoid cells with a

For four days persistent nausea permitted the taking of only liquid foods, and even these were vomited. The pulse became rapid at rest. There had been shortness of breath for five months on any effort but no orthopnea, paroxysmal dyspnea or edema of the ankles.

The patient had complained of vague gastric distress and avoided milk, fruit juice, tomatoes, spinach and other foods. During the present illness, his appetite had been particularly poor and he had lost 20 to 25 pounds (9 to 11 Kg).

**Physical Examination**—On admission the temperature was 38.4 C (101.1 F), the pulse rate 134 per minute, respirations 26 per minute and the blood pressure 100 systolic and 70 diastolic measured in millimeters of mercury. The patient was poorly nourished, pale and sallow with moderate cyanosis of lips and nail beds. There was dyspnea but no orthopnea. The skin and the scleras were icteric. The pulmonary fields were clear. The point of maximum impulse of the heart was felt 11 cm from the midsternal line in the fifth left interspace. No shock or thrill was palpable. The heart rhythm indicated a normal sinus mechanism with occasional premature contractions. At the apex, the first sound was accentuated and a short, high-pitched, systolic murmur was heard. There was no diastolic murmur. After exercise there

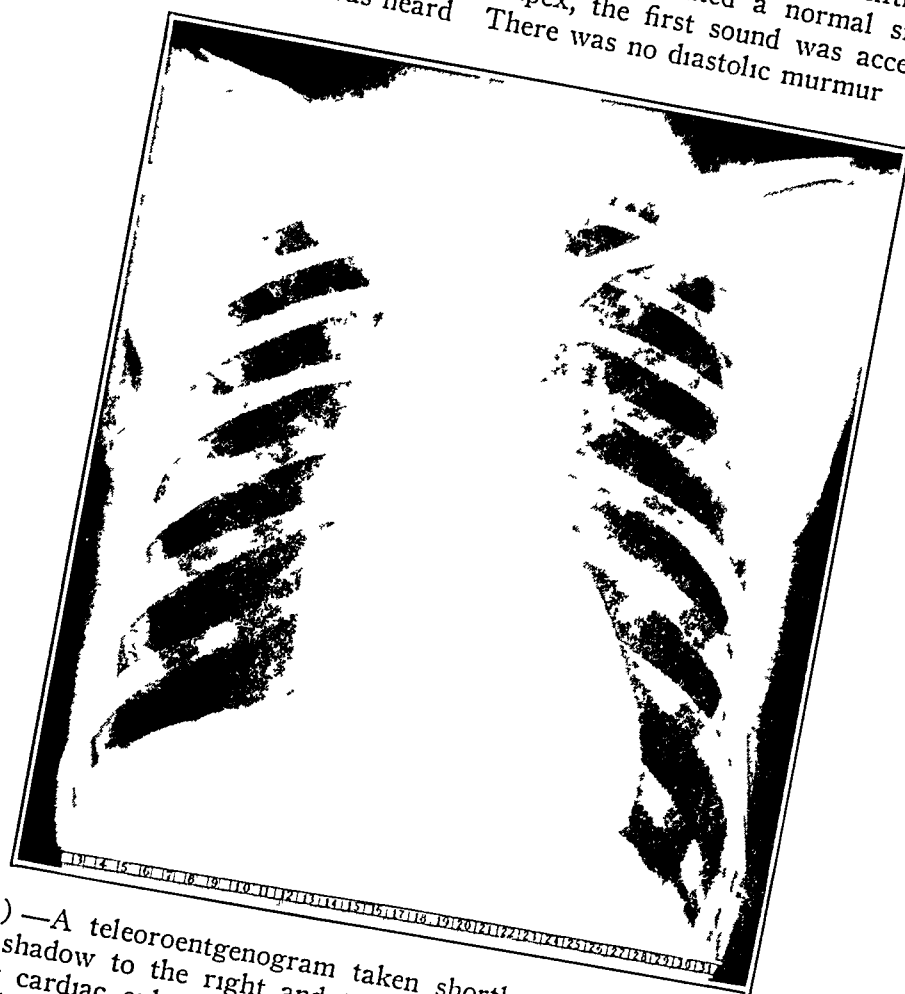


Fig 4 (case 2)—A teleoroentgenogram taken shortly after admission, revealing enlargement of the heart shadow to the right and to the left with straightening of the left cardiac border. The major cardiac enlargement appears to occupy the position of the left ventricle. There is slight fulness in the region of the pulmonary conus. The transverse interlobar fissure on the right is accentuated. Irregular dense shadows are seen throughout both apexes with linear streaking connecting the apexes and the hilar regions.

There were no palpable abdominal viscera, masses, ascites or peripheral edema.

**Laboratory Data**—The specific gravity of the urine was 1.022, there was slight albuminuria, but the sediment was free of cells and casts. Examination of the blood yielded the following data: hemoglobin content, 13.5 Gm per hundred cubic centimeters, red cell count, 5,200,000, leukocyte count, 11,100, with 89 per cent polymorphonuclears, smear, not remarkable, Kline reaction, negative, urea nitrogen, 29 mg per hundred cubic centimeters, sugar, 91 mg per hundred cubic centimeters, cholesterol, 158 mg per hundred cubic centimeters, plasma chlorides, 460 mg per hundred cubic centimeters, and icteric index 19. Four blood cultures were sterile. A van den Bergh test yielded an immediate direct positive reaction, and urobilinogen was present in the urine in a dilution of 1:80. In two hours there was an excretion of 80 per cent of a

*Comment*—This 40 year old Chinese man had symptoms and signs of congestive heart failure with remissions extending over an eight year period. His diet had been deficient at least during the period marked by heart failure. The changes in the skin were those of pellagra, and the lesions about the mouth indicated ariboflavinosis. Appropriate therapy failed to influence the course of illness, and death occurred after the development of erysipelas.

In addition to chronic passive congestion, autopsy showed an enlarged, greatly dilated heart. The conspicuous microscopic change was endocardial fibrosis in addition to myocardial fibrosis, slight focal lymphoid infiltration and vascular engorgement of the myocardium. "Hydropic degeneration," although present, was inconspicuous. Thrombi were encountered in the right auricle and the left ventricle, and a pulmonary infarct was evident.

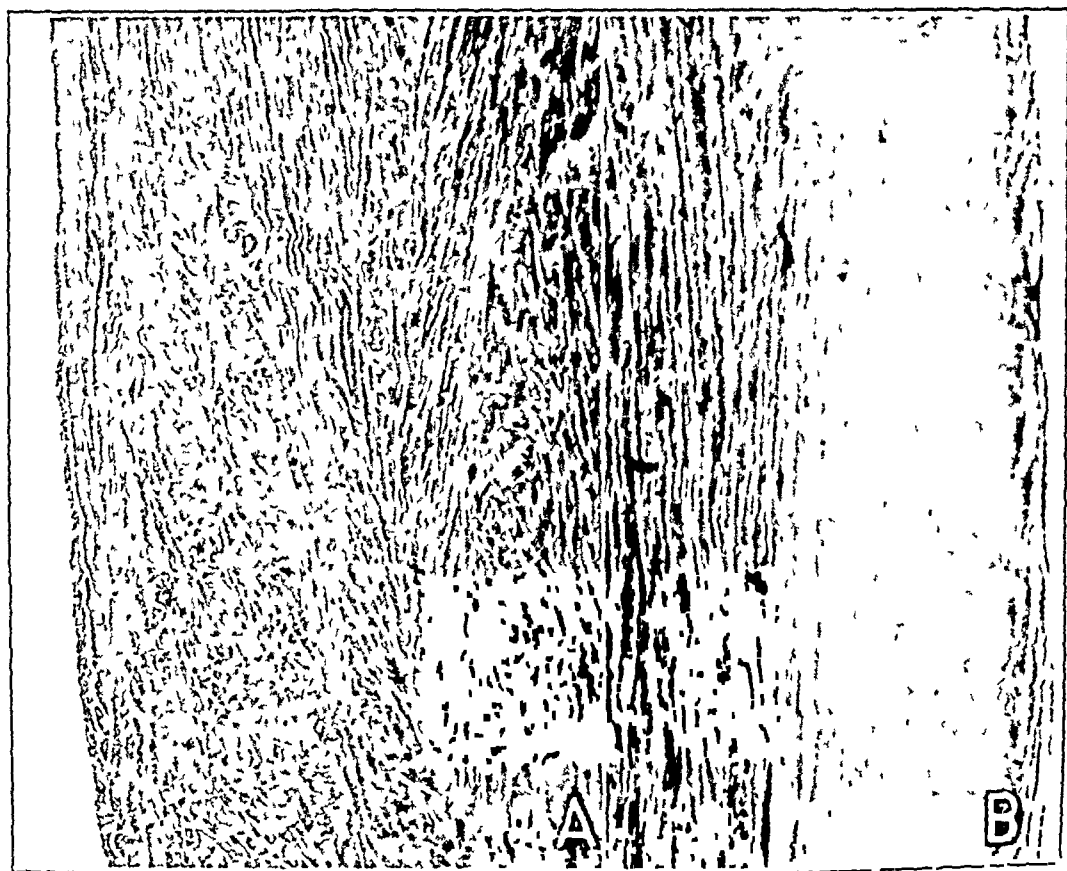


Fig 3—*A*, a section of normal heart muscle, showing the delicate appearance of normal endocardium, measuring only one to two cell layers in thickness. *B*, section of muscle from the heart of the patient in case 1. Contrast the extensive thickening of the endocardium.

**CASE 2—History**—R I, a 35 year old married Italian milliner, was admitted to New York Hospital on Sept 1, 1940, because of dyspnea of five months' duration. At the age of 19 he had had "nephritis" characterized by albumin and casts in the urine which had cleared entirely two years before admission.

The present illness had extended over a nine month period, beginning with nonproductive cough and pain in the anterior portion of the chest on the right side. He had not had hemoptysis or symptoms of pulmonary tuberculosis. Four months after onset he had noted palpitation and a rapid pulse, and a teleoroentgenogram showed slight cardiac enlargement. The patient is said to have received digitalis, quinidine and salicylates for alleged rheumatic carditis.

Two months before admission, while the patient was convalescing, the nonproductive cough had returned. One week before admission dull pain had occurred in the midscapular region.

of the bedclothing leaving pit marks. The patient died quietly on September 11, the tenth day of hospitalization. There had been no response to thiamine or dietary measures.

*Necropsy*—*Gross Examination* The peritoneal cavity contained 500 cc of clear yellowish liquid, but the other cavities did not contain excessive amounts of fluid. The heart weighed 500 Gm. The right auricle was slightly dilated, and its muscular wall was slightly thickened. The wall of the right ventricle measured 5 mm in thickness, and its lumen was moderately enlarged. The myocardium of the left ventricle was not thickened, but the chamber was greatly dilated. Thrombi were encountered in the right auricular appendage and in the columnae carnae of the right ventricle, but in greatest number in the apical half of the left ventricle. The septal endocardium contained large patchy areas of fibrous thickening (fig 5). The valve leaflets were normal. The coronary arteries and the aorta were delicate and free of intimal or medial change. The coronary veins were dilated. There was no evidence of active tuberculosis. No intrinsic lesion of the gastrointestinal tract was encountered.

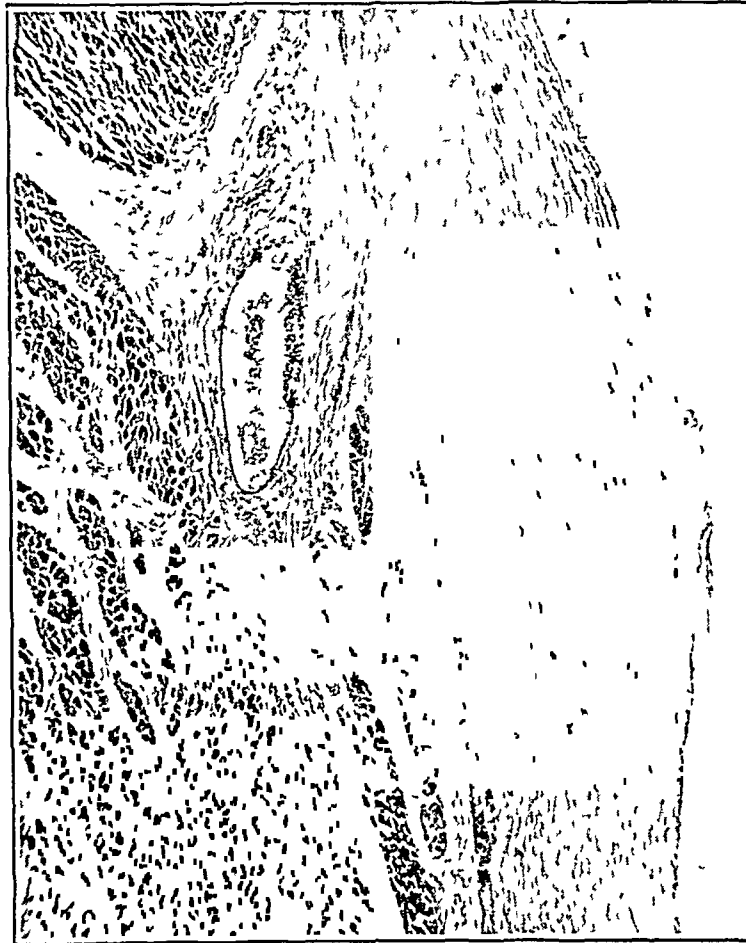


Fig 6 (case 2)—A microscopic section of the myocardium, illustrating the fibrosis of the myocardium and the endocardium. It likewise demonstrates the degenerative change involving the subendocardial fibers with resultant fibrous tissue replacement.

*Microscopic Examination* Section of the heart muscle, distant from the discrete endocardial plaques noted, showed a conspicuous fibrous thickening of the endocardium. Strands arising from the fibrous plate (fig 6) extended deeply into the myocardium. Muscle fibers directly beneath and adjacent to the fibrous plaques showed advanced vacuolization. The incorporation of degenerating subendocardial fasciculi into the fibrous tissue meshwork could be discerned. These fibers stained in unusual fashion with the Masson stain specific for trichomes and with Mallory's stain specific for connective tissue. Organizing thrombi were seen to originate at or close to these areas of fibrosis. In the septum there were several areas of marked interstitial infiltration with polynuclear cells close to the areas of thrombosis at the apex. Sudan III stain revealed numerous small fat droplets in a few myocardial fibers. The capillaries and veins of the myocardium were engorged. There was no change in the vessel walls or in their lumens. In sections of the lung three organizing thrombi and a small recent infarct were seen. The alveolar septums were thickened and ischemic in some places, congested in other places. The liver showed advanced fatty degeneration with necrosis involving the central two



test dose of phenolsulphonphthalein, while urea clearance in 2 tests was 61 and 55 per cent of normal. A roentgenogram (fig 4) outlined a heart enlarged in all diameters with slight fulness of the pulmonary conus. It suggested old bilateral pulmonary tuberculosis with thickened pleura at the right apex. An electrocardiogram showed a right axis deviation. Normal sinus rhythm was present with sinus tachycardia and occasional premature contractions. The T waves were of generally low amplitude in all leads, and the I wave in lead I was abnormal in form. The P wave in lead II was of increased amplitude.

*Course of Illness*—The patient had a low grade fever until shortly before death, the temperature at times being as high as 39.5 C (103.1 F). Food and fluids were limited because of nausea and vomiting. On the fifth day of hospitalization, he complained of pain in the chest on the left side posteriorly and respirations increased to 28 per minute. Over the lower lobe of the left lung there was slight dullness and a few crepitant rales were audible. The radial pulse was feeble, at times imperceptible, the blood pressure was 90 systolic and 70 diastolic measured in millimeters of mercury. At this time the extremities were cold and cyanotic as in peripheral collapse. Cheyne-Stokes respirations were obvious. The obscure picture suggested Addison's disease, and adrenal cortical extract and dextrose in

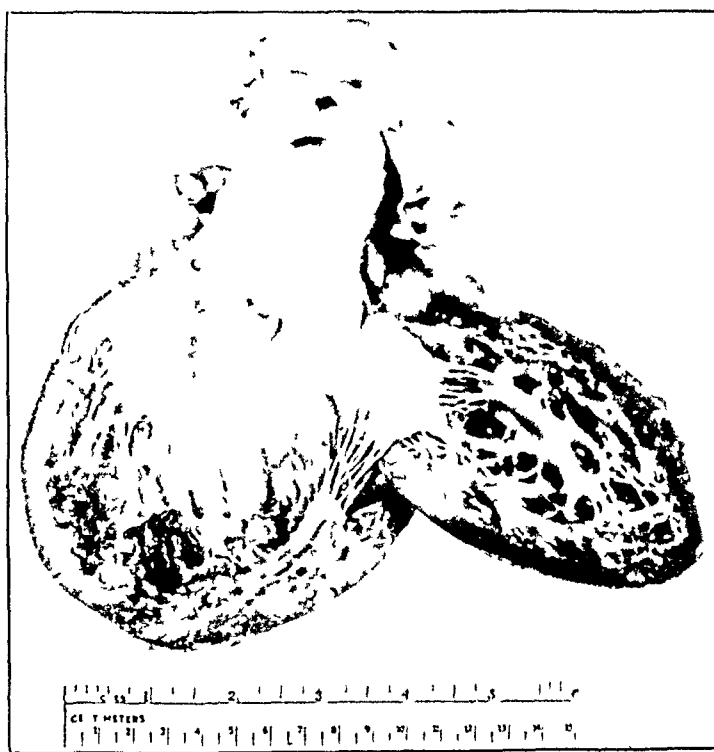


Fig 5 (case 2)—This photograph shows the gross appearance of the heart. There is slight dilatation of the right ventricle and marked dilatation of the left ventricular chamber. Thrombi are seen in the right auricular appendage but in greatest number in the left ventricle. There is a variable degree of organization of these thrombi. The thickening of the endocardium lining the left ventricle is apparent. Several large plaques of endocardial fibrosis are seen, the largest close to the aortic valves.

solution of sodium chloride were administered parenterally in addition to sodium chloride tablets given by mouth, but under this regimen pitting edema of the ankles soon developed. The venous pressure was estimated at 60 mm of blood.

On the seventh day of hospitalization respirations became more embarrassed, and the patient received oxygen therapy. From time to time the shocklike picture reappeared. The blood urea nitrogen rose to 55 mg per hundred cubic centimeters, while the carbon dioxide-combining power was 25 volumes per cent and the icteric index 38. Daily doses of adrenal cortical extract were continued, and thiamine hydrochloride was given daily by vein in 100 mg doses. On the eighth day of hospitalization the skin had a mottled, cyanotic appearance. A tender edge of the liver was palpable 1 fingerbreadth below the costal margin. On the ninth day of his stay in the hospital the patient became stuporous. While the pulmonary fields remained relatively clear, the edge of the liver continued to be palpable. Edema of the ankles was persistent, there was swelling of the eyelids, and the skin was edematous everywhere, pressure

the time. Circulation time measured by sodium hydrocholate was thirty-eight and eight-tenths and thirty-six and two-tenths seconds, while the venous pressure was 172 mm of solution of sodium chloride by direct measurement. An electrocardiogram showed a left axis deviation. The rhythm indicated a normal sinus mechanism. The conduction time of the QRS complex

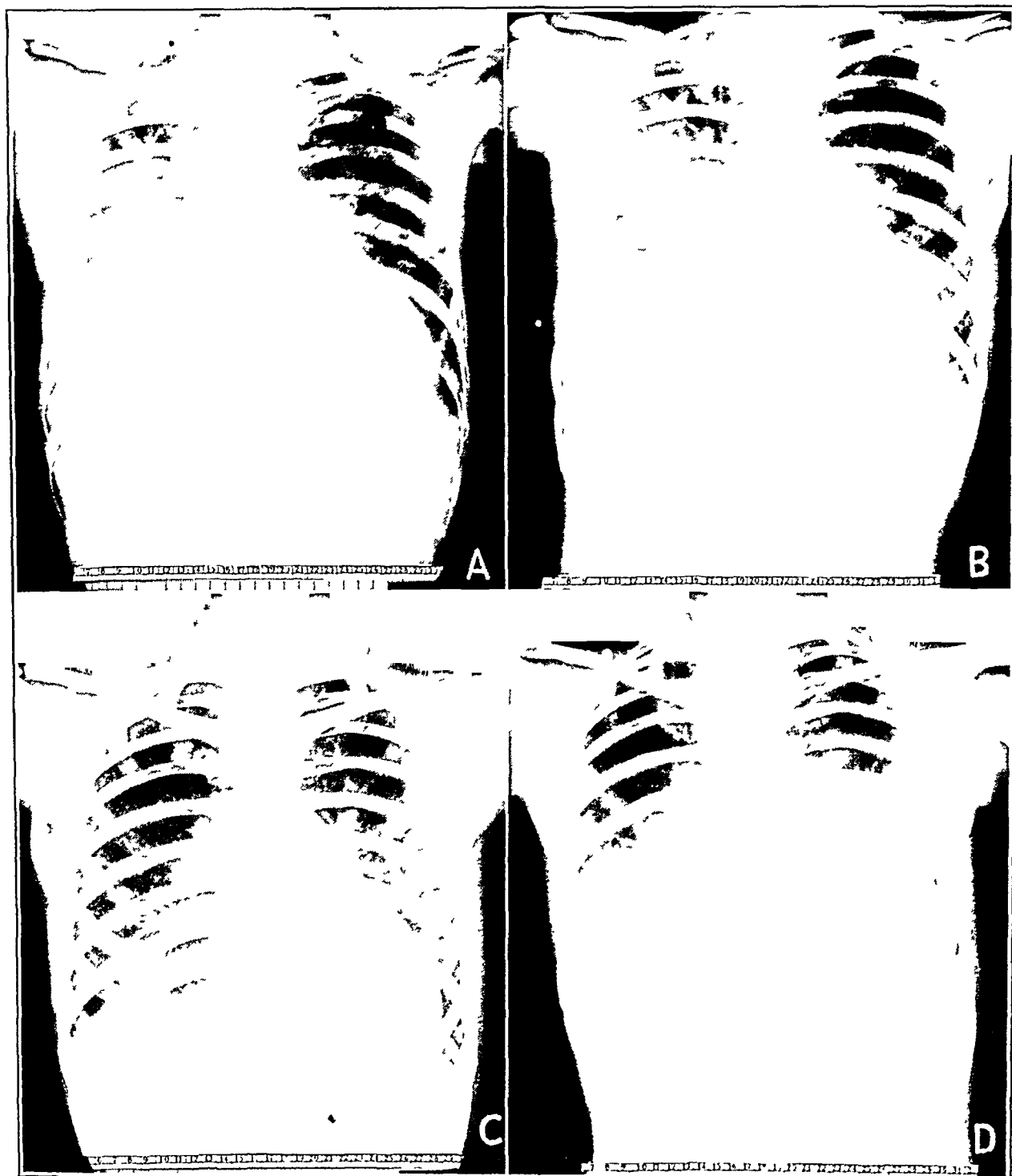


Fig 7 (case 3) —*A*, teleoroentgenogram taken shortly after admission, showing an increase in the transverse diameter of the heart shadow, the enlargement being mostly in the left ventricular area. The pulmonary conus is definitely enlarged. Considerable fluid is accumulated in the right pleural space and extends into the minor fissure of the right side. *B*, a teleoroentgenogram taken after 18 Gm of digitalis was administered within twenty-four hours, showing a decrease in the size of the heart and the pulmonary conus. *C*, a teleoroentgenogram taken at a time when the patient was markedly improved according to clinical standards, showing complete disappearance of the pleural effusion noted in parts *A* and *B*. The cardiac shadow, although smaller, continues to be enlarged, especially the left ventricular portion. *D*, a teleoroentgenogram taken shortly before death, showing the heart shadow to have increased slightly in area. There is again increased density at the base of the right lung.

thirds of the lobule. Much blood pigment had been accumulated in mononuclear phagocytes. There was no renal or adrenal lesion.

*Comment*—This 35 year old man was ill for nine months with obscure complaints largely referable to the gastrointestinal tract. He apparently had been a food faddist for many years, and during the period of final illness his diet was deficient in vitamins. His symptoms were not attributable at once to congestive heart failure, but the palpitation, tachycardia and dyspnea strongly suggested it. The physical findings likewise did not immediately indicate congestive heart failure, although the heart was enlarged. Right axis deviation in the electrocardiogram without demonstrable valvular heart disease was unusual, the alterations in T waves and RT segments were indicative of myocardial change. During his stay in the hospital there were several attacks of peripheral vascular collapse and the patient suffered at least one episode of pulmonary embolism with infarction.

At autopsy the heart was extremely flabby and when suspended by the aorta gave the impression of a paper sac partially filled with fluid. There were thrombi within the chambers of the heart. On microscopic examination the myocardial changes were thought to represent idiopathic isolated myocarditis. Chronic passive congestion involved the lungs, the liver and the heart muscle itself with central necrosis of the liver. There was excess fluid in the peritoneal cavity. The resemblance of the anatomic changes to those in case 1 and the clinical history particularly the poor diet, raise the question whether this case also may be an instance of chronic deficiency of the vitamin B complex.

*CASE 3—History*—R. J., a 35 year old housewife was admitted to New York Hospital on June 24, 1939. One sister had died suddenly at the age of 22. (An incomplete coroner's report stated that there was cardiac hypertrophy with a yellowish myocardium and "myocarditis" was assigned as the cause of death.)

Three months before admission the patient had had an attack of 'bronchitis' with productive cough and pleural pain in the chest on the right side posteriorly. There was no hemoptysis. Occasionally she felt feverish and had night sweats. She became dyspneic and two weeks before admission began to sleep upright. One week before admission she had noted the onset of edema of the ankles followed by swelling of the legs. Two days prior to admission edema had involved the abdominal wall, the lower portion of the chest, the face and the eyes. Although the patient denied that she had any food idiosyncrasy, her husband's account indicated that her intake of vegetables, fruits and meats had probably been borderline. Since the onset of symptoms referable to the respiratory tract she had taken few green vegetables or cereals and little whole grain bread.

*Physical Examination*—On admission the temperature was 37.6 C (99.7 F), the pulse 76 per minute, the respirations 20 per minute and the blood pressure 106 systolic and 88 diastolic measured in millimeters of mercury. The patient was thin and both dyspneic and orthopneic. There was moderate venous distention but no cyanosis. At the extreme base of the right lung there was an area of dullness through which breath sounds were not transmitted. There were a few basal rales bilaterally. The left border of dullness of the heart was 12 cm from the midsternal line in the fifth interspace. The apical impulse was diffuse. There was no thrill palpable. Cardiac sounds were of fair quality, the rhythm indicated a normal sinus mechanism, and no murmurs were heard. The carotid and the brachial pulses were bounding. A tense tender liver was felt 3 fingerbreadths below the costal margin, and the tip of the spleen was just palpable. There were no signs of ascites. No neurologic changes were discovered. There was a moderate pitting edema extending from the ankles over the tibiae and up to the knees with slight pitting edema over the sacrum.

*Laboratory Data*—The specific gravity of the urine varied between 1.006 and 1.032, and specimens showed albumin in moderate amount, but no casts were seen. The urea clearance was 65 per cent of normal. The hemoglobin content of the blood was 11 Gm per hundred cubic centimeters, the red cell count was 4,300,000 per cubic millimeter and the leukocyte count was 7,300 per cubic millimeter. The blood smear and the differential count were not unusual. The corrected sedimentation rate was 0.1 mm (normal 0.4 mm) and the red cell volume 39 per cent. Repeated blood cultures were sterile. The serum per hundred cubic centimeters contained 163 mg of cholesterol, 49 Gm of proteins and 3.4 Gm of albumin. The Kline reaction was negative. Fluid aspirated from the chest had a specific gravity of 1.009. On intravenous administration of 1,000 mg of ascorbic acid 468 mg was recovered in

At no time was hypertension present. Ascites, hepatomegaly, pleural effusion, pulmonary congestion and periorbital and sacral edema continued. The patient showed a marked depressive trend, would not eat and vomited tube feedings. During the last eighteen days of life she received a daily dose of 90 mg of thiamine hydrochloride and 20 Gm of brewers' yeast by mouth. On November 27, the fifty-seventh day after readmission, she died suddenly.

*Necropsy*—The peritoneal cavity contained 1,200 cc of clear liquid, the pericardial cavity 250 cc and the left pleural space 600 cc, while the right pleural space was obliterated by fibrous adhesions. The heart weighed 460 Gm, the wall of the right ventricle measured 4 to 7 mm and that of the left ventricle 12 mm in thickness. The right ventricle was slightly dilated, and its myocardium was moderately fibrosed near the septum, the endocardium in this area was also thickened by fibrous tissue. The left ventricle was dilated, and the anterior, the lower and the septal third showed advanced fibrosis of the myocardium and the endocardium. The fibrosed endocardium measured from 1 to 2 mm in greatest thickness. It encircled papillary muscles and columnae carnae and extended deeply into the myocardium. A large area of the anterior and the apical portion of the endocardium was covered with adherent recent thrombi. Microscopic sections did not show any inflammatory cells. The muscle fibers were thin and appeared atrophic in many places, but striations were well preserved. Some muscle fibers showed a moth-eaten appearance, not like the typical appearance of fatty degeneration which was seen in other areas. Chronic passive congestion was marked in the lungs, spleen, liver and pancreas. The kidneys in addition to chronic passive congestion showed several healed infarcts.

*Comment*—This 35 year old woman was ill for eight months. The onset of her difficulty dated to an infection of the respiratory tract followed by dyspnea, orthopnea, gastrointestinal upset and peripheral edema. Congestive heart failure followed. There was enlargement of the heart, although there was no hypertension or evidence of valvular defect. Berlin heart was considered, but there was little response to administration of thiamine hydrochloride or improved dietary regimen. The patient did not improve with continued administration of digitalis. Mercurial diuretics appeared to aid. Cerebral embolism occurred during her stay in the hospital.

Postmortem examination revealed evidence of congestive heart failure with ascites, hydrothorax and a small hydropericardium (250 cc) and passive congestion of liver, lungs, spleen, kidneys and pancreas. There were organizing mural thrombi within the left ventricular chamber. These led to a cerebral embolus and the renal infarcts. The striking anatomic change was a marked endocardial fibrosis similar to that observed in cases 1 and 2.

#### COMMENT

*Summary of Clinical and Anatomic Findings*—In none of these 3 cases of congestive heart failure was valvular disease, hypertension or arteriosclerosis demonstrable. The patients, 2 men and 1 woman were 35 to 40 years of age. In 1 case symptoms were present during eight years, with the final phase of illness occupying twelve months. In the other 2 cases the patients were ill for eight and nine month periods respectively. In each there was progressive decline modified slightly by therapeutic measures. One patient a Chinese man (case 1) had lived on a deficient diet over a long period, the other 2 patients had "poor appetites" and had taken diets probably borderline in their content of the vitamin B complex. In all cases the diet was deficient after the onset of the final illness.

The symptoms and signs on admission and during hospitalization pointed to disease of the cardiovascular system. Cyanosis was noted in 2 patients on admission and appeared in the third patient during hospitalization. Various other phenomena of congestive heart failure were observed with prolongation of circulation time and increase of venous pressure in 2 patients.

All patients showed albuminuria probably related to chronic passive congestion, and the serum protein levels of 2 patients were 5.9 Gm per hundred cubic centi-

in lead II measured twelve hundredths of a second, and the I waves and the R1 segments had the form seen in the left intraventricular heart block of the concordant type. The P waves were notched in all leads. Teleorontograms made in this case are reproduced in figure 7.

*Course of Illness*—Throughout her stay in the hospital the patient had a low grade fever. A diet high in vitamins and in carbohydrate was attempted, but because of refusal to eat tube feedings of high vitamin content had to be employed over a long period. The diagnosis of beriberi heart was proposed, and thiamine hydrochloride was given intravenously in 10 mg doses daily for the first five days and then 20 mg a day for the succeeding thirty-eight days with 8 Gm of brewers' yeast daily. Nevertheless, dyspnea increased and the patient became cyanotic, so that an oxygen chamber was employed. While this afforded slight relief, more marked improvement was noted with mercurpurin therapy. Finally digitalis was given. The day following the circulation time was twenty-seven and six-tenths and twenty-eight and six-tenths seconds and the venous pressure was 117 mm of solution of sodium chloride. Two days after digitalization a complete left hemiplegia suddenly developed. The pressure and composition of the spinal fluid were normal. Under the usual supportive measures there was a return of



Fig 8 (case 3)—A microscopic section of the myocardium, illustrating fibrosis of the endocardium and myocardium.

strength in the legs and arms, the deep tendon reflexes became normal and the sensory modalities returned, but weakness of the left side of the face and the plantar extensor response on the left side persisted. The phenomena of congestive heart failure cleared, and digitalis and diuretics were discontinued. Edema did not recur. The patient then tolerated restricted activity about the ward and finally was allowed home on the eighty-fourth day of her stay in the hospital. Within a few days she was readmitted with oliguria and dyspnea. There was edema of the face and dependent parts. The venous pressure was estimated at 150 mm of solution of sodium chloride. A soft systolic murmur was heard at the apex. There was ascites. The liver was palpable 3 fingerbreadths below the costal margin. The blood picture was unchanged. The electrocardiographic pattern was little altered throughout the whole course of illness. Left intraventricular heart block continued to be present, and there was little change in the form of the T waves or the RT segments. Premature contractions of auricular, auriculoventricular nodal and ventricular origin were frequently recorded.

On the twelfth day after readmission the patient had a generalized convulsion lasting for three minutes, and on the thirty-fourth day this was repeated. There were no residual signs

*Isolated (Fiedler's) Myocarditis*—Survey of the papers dealing with isolated myocarditis has failed to establish a uniform clinical or pathologic syndrome. Steffen<sup>5</sup> in 1888 reported the first cases of a condition designated acute myocarditis. In 1890 Fiedler<sup>6</sup> delineated the syndrome now bearing his name, while the adjective isolated was included by Sellentin<sup>7</sup> to indicate absence of inflammatory changes elsewhere. Aschoff<sup>8</sup> stated that he considered the lesions to be rheumatic in origin. In a search of the literature Scott and Saphir<sup>9</sup> found 36 reports with postmortem findings and tabulated the pertinent data in 30 cases. Bailey and Andersen<sup>10</sup> in their report reviewed this series, with criticisms. Thus, in the case reported by Rindfleisch<sup>11</sup> the condition probably was multiple pyogenic abscesses of the myocardium, in the second case of Steffen<sup>5</sup> and in the case reported by Baumgartner<sup>12</sup> the patient may well have had tuberculosis. Since the paper of Bailey and Andersen<sup>10</sup> many other reports have appeared.<sup>13</sup> In a recent review von Bonsdorff<sup>14</sup> indicated that in several of these<sup>13</sup> the classification of acute isolated myocarditis is not warranted. Several patients died suddenly after an acute illness, in others the course was chronic and marked by protean manifestations. In the former group careful histologic search disclosed small focal cellular infiltrations in the myocardium. In the cases in which illness was more chronic autopsy revealed varying pictures. A clear anatomic concept was not

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meters (case 1) and 4.9 Gm per hundred cubic centimeters (case 3). In these same 2 patients, the first with clinical pellagra and ariboflavinosis, the administration of 1,000 mg of ascorbic acid intravenously resulted in the excretion of 31 mg and 468 mg, respectively.

Electrocardiograms were altered, but no characteristic changes were observed. In case 1 auricular fibrillation was present, in the others normal sinus rhythm prevailed. In 2 cases there was right axis deviation. Left intraventricular heart block of the concordant type was present in the third case. Those patients with normal sinus mechanism showed various irregularities of rhythm. Premature contractions of ventricular origin occurred in case 2, in case 3 there were premature contractions, arising singly and in combination from the auricle, the auriculoventricular node and the ventricular muscle. Tall, notched P waves were seen in case 3. Alteration in the form of the T waves and the RT segments in each case pointed to myocardial change.

Several teleoroentgenograms, including anteroposterior and lateral views, were made at a 2 meter distance in each case. In case 1 (fig 1) the shadow of the heart was tremendously enlarged in all diameters, particularly that of the left ventricle, and the pulmonary conus appeared full. A small amount of liquid obscured the left costophrenic angle. The heart shadow in case 2 (fig 4) was increased to the right and the left with a straightening of the left cardiac border, the left ventricle constituting the major enlargement. On the first roentgen examination in case 3 (fig 7A) the transverse diameter of the heart was increased, the enlargement being mainly left ventricular, and the pulmonary conus was so prominent that mitral stenosis was suggested. Considerable fluid was apparent in the right pleural space with extension into the minor fissure. Further roentgen studies after digitalization (fig 7B and C) showed a slight and transient change in the cardiac outline. All patients had received digitalis without significant salutary effect. In 1 case the velocity of blood flow was enhanced by administration of the drug, the circulation time decreasing from thirty-seven and five-tenths seconds to twenty-eight and one-tenth seconds (average), while the venous pressure was lowered from 172 mm to 117 mm of solution of sodium chloride. These physiologic adjustments were not accompanied by clinical improvement, and the patient suffered cerebral embolism shortly after full digitalization. In the 2 cases (1 and 3) in which mercupurin was administered satisfactory diuresis, disappearance of edema with parallel loss in body weight and clinical improvement were noted. None made significant response to thiamine hydrochloride, nor was diuresis observed when the drug was given intravenously in doses ranging from 20 to 100 mg over various periods. The course of illness was marked by progressive congestive heart failure with embolic phenomena.

The principal findings at necropsy in these cases agreed in several respects. In each there was evidence of cardiac failure with chronic passive congestion of the viscera. Pulmonary infarction was encountered in 2 cases, while in the third there were small renal infarcts. The heart was enlarged in each case, weighing 650, 500 and 460 Gm, respectively. The degree of hypertrophy and dilatation with respect to individual chambers has been described. Mural thrombi with varying degree of organization were seen in both right and left ventricles in 2 cases, while the left ventricle alone was involved in the third. There was no anatomic evidence of valvular defect, hypertension, arteriosclerosis or syphilis. Myocardial fibrosis was the conspicuous microscopic change. The most marked feature in all cases was the widespread endocardial fibrosis in both right and left ventricles, varying in its extremes from plaque-like deposits in case 2 and case 3 to the formation of a dense fibrous tissue plate covering the myocardium and investing the papillary muscles and trabeculae carneae in case 1.

to a deficiency of vitamin B complex. He reasoned that vitamin B<sub>1</sub> failed as a therapeutic agent, remissions occurred without the use of vitamin B<sub>1</sub> (in addition to the general hospital diet) and that the pathologic lesion was not like that of beriberi. In all of our cases there were remissions without therapy with the vitamin B complex. In the first case remissions were characteristic of an eight year period of illness. Moreover, none of our patients made significant response to thiamine hydrochloride in recommended dosage. The patient in the first case reported by Levy and Rousselot<sup>22</sup> had "slight thickening of the septal surface of the endocardium which at this place measured 2 mm." In their second case the condition might represent the intermediate stage between the acute form of beriberi heart and the more chronic disease being described in this report. The fibers of the heart muscle showed an advanced stage of hydropic degeneration. Vacuolization was so pronounced that "only a little remnant of sarcoplasm remained against the cell membrane making the muscle fibers appear as empty envelopes" (figures 5 and 6 of the paper by Levy and Rousselot<sup>22</sup>). There was advanced fibrosis, "everywhere throughout the heart, the knife, as it cut, encountered unusual resistance." Thickening of the endocardium was conspicuous as "it was no longer possible to see the underlying myocardium." In their third case there were "thin streaks of endocardial thickening over the interventricular septum." In all cases there were mural thrombi in the ventricles and pulmonary and systemic infarcts. The authors did not review their patients' dietary habits. Kugel and Stoloff<sup>25</sup> described 7 cases of "idiopathic hypertrophy of the heart" in infants, noting endocardial fibrosis in all of them. These authors suggested that among other causes "history of avitaminosis (beriberi)" ought to be excluded. Endocardial fibrosis was described in one of Sellentin's protocols<sup>7</sup> as early as 1904. The formation of mural thrombi is probably facilitated by the plaque-like thickenings of endocardium and may mark a terminal stage in the disease process. The problem is whether myocardial fibrosis represents a late stage in the development of beriberi heart.

*Experimental Production of Beriberi Heart*—Attempts to produce cardiac lesions in experimental animals by diets deficient in the vitamin B complex have not been entirely successful. Lack of knowledge of spontaneous myocarditis and of changes due to vitamin deficiency in animals limit such observations. Miller<sup>26</sup> encountered myocardial lesions in 60 per cent of a rabbit colony which was presumably healthy. Thomas, Mylon and Winternitz<sup>27</sup> produced myocardial lesions by keeping rats and pigs on a diet deficient in potassium as well as in the vitamin B complex. It is possible that in the pathogenesis of chronic beriberi heart factors other than a deficiency of thiamine hydrochloride participate. Swank<sup>28</sup> found that in about half of the hearts of pigeons "chronically deficient in thiamin, early changes were evident, such as focal necrosis with inflammatory cell infiltration." Porto and de Soldati,<sup>29</sup> studying cardiac changes in rats and dogs, reported "anemic infarcts" together with interfascicular edema, perinuclear vacuolization

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possible on careful review of Friedler's original case reports.<sup>6</sup> Karsner<sup>15</sup> defined acute isolated myocarditis as a

disease principally of early middle life, with insidious onset, signs of cardiac insufficiency and death after the lapse of a few months. The heart is hypertrophic, but without lesions of endocardium or pericardium. Microscopically there is interstitial infiltration of lymphocytes, leukocytes and large mononuclears with variable degrees of muscle destruction.

Most authors, including Scott and Saphir, have employed similar criteria. Nevertheless, in the first of the cases reported by Scott and Saphir there were thrombi in the mural endocardium of the right ventricle, and in their second case thrombi were encountered in the left ventricle "where a few circumscribed areas of endocardial fibrosis were seen." The case report of de la Chapelle and Graef<sup>13b</sup> stated that "the endocardium was intact throughout, except at the apex of the left ventricle, where a firm, grayish-red thrombus was found attached to the endocardium." The microscopic examination of a section from the apex of the left ventricle "revealed a fairly advanced organizing process." For the most part these authors have included little detail of the patient's dietary habits.

*Etiologic Factors*—The attempt to assign a common etiologic basis to "Friedler's myocarditis" has likewise been unsuccessful. The role of infection of the respiratory tract has been emphasized in the earliest reports, but recent studies suggest many other factors. The myocardial disease in the case reported by Maxwell and Barrett<sup>13c</sup> followed a severe dermatitis due to sulfur ointment and was associated with staphylococcic bacteremia. Brown and McNamara<sup>14</sup> called attention to 8 cases of "acute interstitial myocarditis" following the administration of arsphenamine and reviewed the reports of Nelson,<sup>15</sup> Sikl,<sup>16</sup> von Zalka,<sup>17</sup> Stoeckenius<sup>18</sup> and Taussig and Oppenheimer.<sup>19</sup> A similar case apparently resulting from arsenical therapy for syphilis during pregnancy was observed in this hospital and another case resembling the one reported by Guizzetti<sup>14d</sup> characterized by myocardial edema and lymphocytic infiltration, occurred in a young diabetic patient with Friedreich's ataxia.<sup>20</sup> In a recent review on myocarditis by Saphir<sup>21</sup> including Friedler's myocarditis, the possible association with nutritional deficiency is not suggested.

*Beriberi Heart and "Idiopathic" Cardiac Hypertrophy*—Certain cases previously reported as isolated myocarditis might have been classified as beriberi heart had more detailed information been available. Dock<sup>1</sup> described such lesions as we have encountered, including the endocardial fibrosis, although it was not so widespread. Similar cases were reported by Levy and Rousselot<sup>22</sup> and by Levy and von Glahn,<sup>23</sup> although they were interpreted differently. In comment on Dock's paper Levy<sup>24</sup> denied the relation of illness in the cases which he reported

15 Karsner, H. T. Human Pathology, ed. 4, Philadelphia, J. B. Lippincott Co., 1935, p. 460.

16 Sikl, H. Eosinophile Myocarditis als idiosynkrasische-allergische Erkrankung, Frankfurt Ztschr. f. Path. **49** 283, 1936.

17 von Zalka, E. Ueber einen seltsamen Fall von Polymyositis, Virchows Arch. f. path. Anat. **281** 114, 1931.

18 Stoeckenius, W. Beobachtungen an Todesfallen bei frischer Syphilis. Beitr. z. path. Anat. u. z. allg. Path. **68** 185, 1921.

19 Taussig, H. S., and Oppenheimer, E. H. Severe Myocarditis of Unknown Etiology, Bull. Johns Hopkins Hosp. **59** 155, 1936.

20 Unpublished data.

21 Saphir, O. Myocarditis. A General Review with an Analysis of Two Hundred and Forty Cases, Arch. Path. **32** 1000 (Dec.) 1941, **33** 80 (Jan.) 1942.

22 Levy, R. L., and Rousselot, L. M. Cardiac Hypertrophy of Unknown Etiology in Young Adults, Am. Heart J. **9** 178, 1933.

23 Levy, R. L., and von Glahn, W. C. Further Observations on Cardiac Hypertrophy in Adults, Tr. A. Am. Physicians **52** 259, 1937.

24 Levy, R. L., in discussion on Dock.<sup>1</sup>

The observations here described suggest that it may also be the end result of nutritional deficiency. Investigation must still ascertain whether the subendocardial fibers are more susceptible to hydropic degeneration and whether fibrosis supervenes hydropic degeneration. It is possible that endocardial and myocardial fibrosis may render the disease process self aggravating and self perpetuating in the nature of a vicious cycle. Muscle degeneration leads to fibrosis and in turn to further degeneration of enclosed muscle fibers, aggravated by rhythmic stretching of the heart, produced or facilitated by some factor not yet recognized. It is conceivable that some myocardial functional change coexists with a nutritional deficiency, for example, the stimulus of diastolic stretching may fail to elicit the usual response leading to hypertrophy when the muscle fibers are injured by hydropic degeneration but interstitial fibrosis once established may in itself be an aggravating factor. Wearn<sup>1</sup> reviewed the communication of vessels in the myocardium with the ventricular cavities, designating them as "arterio-luminal" and "arterio-sinusoidal." A diagram of Wearn's has been modified to show the impairment of blood supply as a consequence of endocardial fibrosis (fig 9).

Whether the cases here described actually represent chronic beriberi heart, or are at all the consequence of nutritional deficiency, is not adequately proved. The clinical and anatomic findings parallel previously reported instances of isolated (Fiedler's) myocarditis. Study of the reported cases indicates that "isolated myocarditis" represents a heterogeneous collection of acute and chronic forms of myocardial disease marked by inflammatory or degenerative changes with and without fibrosis. Further separation of the complex into well defined types is desirable. Evaluation of available data suggests that the 3 cases outlined here represent a chronic form of heart disease, possibly caused by or associated with dietary deficiency. The purpose of this report is to call attention to this type and to stimulate further inquiry into its pathogenesis.

#### SUMMARY

Three cases of heart failure in young adults which is not attributable to arteriosclerosis, hypertension or valvular heart disease are reported.

The most striking pathologic features are endocardial and myocardial fibrosis and cardiac hypertrophy and dilatation in the absence of vascular or valvular change. The endocardial fibrosis and cardiac failure predispose to mural thrombosis with emboli. These changes resemble those previously described in the literature under the term isolated myocarditis.

The question is raised whether these changes could have been associated with deficient diet and could represent a variant of beriberi heart.

NOTE—Since preparation of this manuscript 2 additional cases have been encountered.

CASE 4—A 63 year old bachelor, chronically addicted to alcohol, with irregular eating habits, gave evidence of congestive heart failure extending over four years. At autopsy there were endocardial and myocardial fibrosis, mural thrombosis and pulmonary infarction.

CASE 5—A 54 year old man with "poor" appetite and "chronic indigestion" of twenty years' duration gave a history of ten years of marked chronic alcoholism. Symptoms of heart failure extended over three years. At autopsy the heart was dilated and showed myocardial and endocardial fibrosis, while the coronary arterial bed was entirely normal on examination, which included injection. Mural thrombosis of the right ventricle had led to pulmonary infarcts.

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and marked vacuolization of the conduction system Leblond and Chaulin-Serviniere<sup>30</sup> studied beriberi in monkeys and concluded that partial rather than complete thiamine deficiency was the cause of chronic heart disease

*Clinical and Anatomic Features of Beriberi Heart*—Cardiac failure in beriberi has been explained by Wenckebach<sup>2</sup> with the myogenic, as opposed to the neurogenic, theory He postulated that the heart muscle lost its power of contraction and its resistance against stretching In the cases which he reported the right ventricle, especially the conus arteriosus, was dilated, while the left ventricle did not appear to have been overloaded There is a lowered peripheral resistance with rapid stasis of blood in the capillaries at the arteriolar end The systolic energy is not decreased and the right side of the heart is filled under high venous pressure, "the blood runs to the heart in an attempt to burst it apart" (Wenckebach) The clinical picture is, however, not always so clear Keefer,<sup>1</sup> studying beriberi in China, indicated that dilatation was not limited to the right ventricle Weiss and Wilkins<sup>3</sup> likewise noted pulmonary engorgement with dyspnea and orthopnea and other evidence of "left sided failure" These authors did not regard peripheral neuritis as a necessary accompaniment of such deficiency

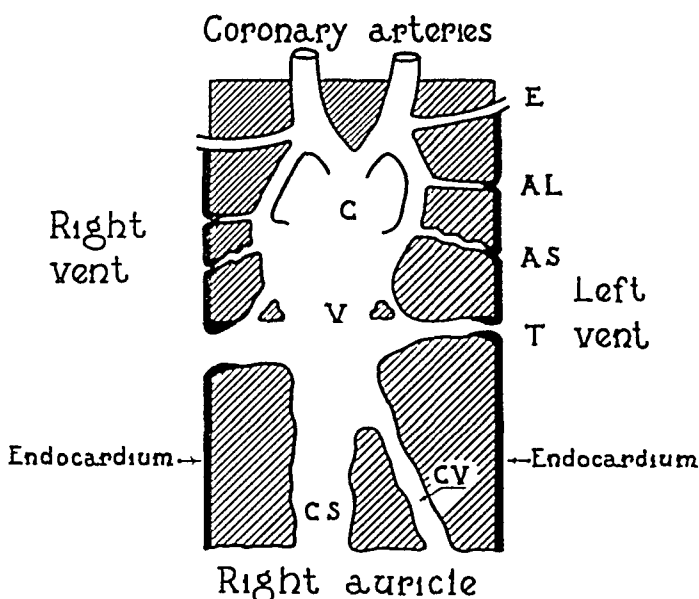


Fig 9—Wearn's schematic representation of the coronary circulation is here modified to include thickening and fibrosis of the endocardium The effect of such change on the nutrition of the myocardium is apparent The following abbreviations have been employed *E*, extra-cardiac branches, *AL*, arterioluminal vessels, *AS*, arteriosinusoidal vessels, *T*, thebesian veins, *V*, coronary veins, *CV*, coronary veins, and *CS*, coronary sinus

In the 3 cases reported here a clinical syndrome with fairly uniform features was present The usual precipitating causes of heart failure were notably absent Careful questioning elicited the history suggestive of dietary deficiency, but accurate studies of absorption and utilization of the vitamin B complex were not possible Autopsy revealed the features of congestive heart failure The hearts were enlarged and dilated Mural thrombosis had occurred and had led to embolism Myocardial fibrosis has usually been ascribed to diminution of the myocardial blood supply<sup>32</sup> leading to scattered areas of degeneration and replacement fibrosis

30 Leblond, C P, and Chaulin-Serviniere, J Spontaneous Beriberi of the Monkey as Compared with Experimental Avitaminosis, *Am J M Sc* **203** 100, 1942

31 Keefer, C S The Beriberi Heart, *Arch Int Med* **45** 1 (Jan) 1930

32 White, P D Heart Disease, ed 2, New York, The Macmillan Company, 1937, pp 427-428

as can be determined, infections due to members of groups E, H and K have not been reported

Group C organisms are probably responsible for more infections than organisms of any group other than A.<sup>2b</sup> It is not to be inferred, however, that group C strains are common in relation to members of group A, which cause over 95 per cent of all streptococcic infections. Less than 100 cases of infection caused by group C organisms are recorded in contrast to the many thousands of infections caused by group A organisms that can be found in the literature. Scarlet fever,<sup>2b</sup> puerperal infection,<sup>10</sup> erysipelas<sup>11</sup> and infections of wounds<sup>2b</sup> are the chief conditions in which group C organisms have been isolated. A knowledge of the natural distribution of these organisms is important in evaluating their role in infections in human beings. In general, it can be said that in normal persons group C strains are isolated from the same sources as are members of group A but much less frequently. For example, hemolytic streptococci of group A are recovered from the normal human nasopharynx three or four times as often as are hemolytic streptococci of group C.<sup>12</sup>

The purpose of this paper is to present a case of bacteremia in which hemolytic streptococci of group C were the infectious agents and in which recovery followed administration of sulfadiazine. In addition, bacteriologic and immunologic data will be presented and will be discussed in relation to the Lancefield groups as a whole.

#### REPORT OF CASE

*History*—The patient was a 65 year old single white American janitor, who entered Stanford University Hospitals on Nov. 1, 1941, complaining of generalized pains and shortness of breath of several months' duration. The history was not considered entirely complete or reliable because of the patient's faulty memory for recent events.

The familial history and the past history were not contributory. The patient was well and strong until about five months before admission, when he had an episode of vomiting and diarrhea, which he attributed to eating poisoned meat. After this he refused to eat meat, but his diet was otherwise probably adequate. He felt certain that this episode marked the beginning of his present illness. Easy fatigability and dyspnea on the slightest exertion appeared almost immediately. Generalized "pains in the muscles" also appeared, which were deep and "felt as if they were in the bones," especially in the legs.

Two months before entry he suddenly noted a sharper, more constant pain in the left hip, which caused limitation of motion of that joint. This occurred at intervals until the time of entry. General fatigue, muscle aches and shortness of breath became gradually more pronounced, although he remained ambulatory. Thirteen days before admission he was seized with a sharp, severe pain in the chest on the left side, just below the nipple, which radiated to both axillae and caused difficulty in breathing. He sat up all night, and the next morning his pain gradually disappeared. After this episode, he became weaker and the muscular pains became more pronounced. One week before entry he had a moderately severe shaking chill, the first he had experienced. Chilly sensations recurred at intervals during the next several days, but he was not aware that he had any fever. At the time of admission there was a superficial ulcer on the left thigh, which he had not noticed. Moderate tenderness over the left parotid region had been present for several days. A loss of weight of 10 to 15 pounds (5 to 7.5 Kg) was said to have occurred during the past four or five months.

*Physical Examination*—On admission the patient was slender, poorly nourished and acutely ill. The temperature was 40 C (104 F), the respirations were 22 per minute, the pulse rate was 84 per minute, and the blood pressure was 150 systolic and 80 diastolic. Small, pinkish red, maculopapular lesions were irregularly scattered over the skin of the entire body.

10 Congdon, P. M. Streptococcal Infection in Childbirth and Septic Abortion. Source of Infection and Grouping of Hemolytic Strains, *Lancet* **2** 1287, 1935. Rosenthal and Stone.<sup>5</sup>

11 Hare, R. The Classification of Hemolytic Streptococci from the Nose and Throat of Normal Human Beings by Means of Precipitin and Biochemical Tests, *J. Path. & Bact.* **41** 499, 1935. Plummer, H. Serological Study of Hemolytic Streptococci, *J. Bact.* **30** 5, 1935.

12 (a) Rantz, L. A. The Hemolytic Streptococci. Studies on the Carrier State in the San Francisco Area, with Notes on the Methods of Isolation and Serological Classification of These Organisms, *J. Infect. Dis.* **69** 248, 1941. (b) Hare.<sup>2b</sup>

# STREPTOCOCCIC BACTEREMIA CURED WITH SULFADIAZINE

REPORT OF A CASE OF INFECTION CAUSED BY HEMOLYTIC STREPTOCOCCI  
OF LANCEFIELD GROUP C WITH A REVIEW OF THE LITERATURE  
AND PRESENTATION OF IMMUNOLOGIC DATA

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The classification of hemolytic streptococci proposed by Lancefield<sup>1</sup> in 1933 has proved an important advance in the study of streptococcal infections. Using the precipitin technique based on the presence in hemolytic streptococci of a specific carbohydrate obtainable by acid hydrolysis, she divided these organisms into several groups, designated by the letters A to K inclusive and pointed out that most streptococcal infections in human beings were caused by members of her group A. Subsequent studies have confirmed this observation - but a good many cases have been reported in which etiologic organisms were members of certain of the other groups.

Group B strains have been isolated in cases of suppurative arthritis,<sup>3</sup> puerperal sepsis<sup>4</sup> and endocarditis.<sup>5</sup> Severe cases of endocarditis<sup>6</sup> and puerperal sepsis<sup>41</sup> have also been ascribed to members of group G. The status of group D organisms is beyond the scope of this paper and will be discussed elsewhere.<sup>7</sup> Although frequently recovered from patients their role in the causation of disease is often difficult to ascertain. Group F strains have been isolated from infected wounds and sinuses<sup>8</sup> and from the throats of patients with glomerulonephritis.<sup>9</sup> As far

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From the Department of Medicine, Stanford University School of Medicine

1 Lancefield, R C. A Serological Differentiation of Human and Other Groups of Hemolytic Streptococci, *J Exper Med* **57** 571, 1933

2 (a) Rantz, L A, and Keefer, C S. The Distribution of Hemolytic Streptococci Groups A, B, and C in Human Infections, *J Infect Dis* **68** 128, 1941 (b) Hare, R. Sources of Hemolytic Streptococcal Infection of Wounds, *Lancet* **1** 109, 1940

3 Rantz, L A. Suppurative Arthritis Due to a Hemolytic Streptococcus of the Lancefield Group B. A Case Report, *Ann Int Med* **13** 1744, 1940

4 (a) Lancefield, R C, and Hare, R. Serological Differentiation of Pathogenic and Non-Pathogenic Strains of Hemolytic Streptococci from Parturient Women, *J Exper Med* **61** 335, 1935 (b) Frv, R M. Fatal Infections by Hemolytic Streptococcus Group B, *Lancet* **1** 199, 1938

5 Rosenthal A H, and Stone, F M. Puerperal Infection with Vegetative Endocarditis, *J A M A* **114** 840 (March 9) 1940

6 MacDonald, I. Fatal and Severe Human Infections with Hemolytic Streptococci Group G (Lancefield), *M J Australia* **2** 471, 1939

7 Rantz, L A, and Kirby, W M M. Enterococcal Infections. An Evaluation of the Importance of Fecal Streptococci and Related Organisms in the Causation of Human Disease, *Arch Int Med* **71** 516 (April) 1943

8 Longcope, W T. Studies of the Variations in the Antistreptolysin Titer of the Blood Serum from Patients with Hemorrhagic Nephritis. II. Observations on Patients Suffering from Streptococcal Infections, Rheumatic Fever and Acute and Chronic Hemorrhagic Nephritis, *J Clin Investigation* **15** 277, 1936

9 Long, P H, and Bliss, E A. Studies upon Minute Hemolytic Streptococci. IV. Further Observations upon the Distribution of Ordinary and Minute Beta Hemolytic Streptococci in Normal and Diseased Human Beings, *J Infect Dis* **62** 52, 1938

moderate rise in the red cell and the white cell count, the blood picture remained much as it was on admission. A biopsy of bone marrow was done two weeks after entry, and the marrow was found to be hypoplastic. Inactivity of myelocyte multiplication, with delayed maturing of these cells to the polymorphonuclear stage, appeared to be the chief cause for the hypoplasia of the white cell series. Except for moderate weakness the patient felt entirely well when he went home on the eighteenth day after admission.

His subsequent course was followed in the outpatient department for twelve weeks, and during this time he was afebrile, and his only complaints were easy fatigability and precordial pain and dyspnea on exertion. The blood picture remained essentially unchanged, except that the red cell and the white cell count fell gradually, in spite of intensive therapy with various preparations of iron and liver. A roentgen survey of the long bones during this period did not reveal any abnormalities.

The patient reentered the hospital during the fifteenth week after the first admission. Physical examination failed to reveal anything new, except for a fissure *in ano*, which was painful. The results of laboratory examination were as follows: red cell count, 1,052,000; hemoglobin concentration, 34 per cent; white cell count, 1,400, with a differential count of polymorphonuclear leukocytes 16 per cent (64), lymphocytes 74 per cent and monocytes 16 per cent; hematocrit reading, 14; platelet count, 18,000; reticulocyte percentage, 0.3; urine and stool normal; Bence Jones protein in urine, none; and blood urea, 33 mg per hundred cubic centimeters.

Two blood transfusions were given, after which the red cell count rose to 2,200,000. The patient was then transferred to another hospital. Within two days his temperature began to rise, and a blood culture was positive for *Escherichia coli*. The septic process continued in spite of therapy with sulfadiazine and transfusions, and the patient died sixteen weeks after the onset of the bacteremia caused by hemolytic streptococci.

*Autopsy*—Results of a postmortem examination contributed little. The bone marrow presented the same hypoplastic picture which was seen in the biopsy specimen. No other significant lesions were encountered.

*Comment*—The cause of the aplastic anemia is not known, but it is quite certain that the streptococcic infection was not responsible. The patient had had symptoms of the underlying disease for two or three months before chills and fever appeared, suggesting that the bacteremia was an intercurrent episode, made possible partly by a lowering of the natural cellular defense mechanisms. Further, an aplastic blood picture is rarely if ever produced by acute infections. The absence of an elevation of blood bilirubin suggests that no acute hemolytic process had occurred. Finally, the bone marrow did not resume its normal activity after the infecting organisms had been cleared from the blood stream, indicating that the depression of hemopoietic activity was caused by some other agent.

The response to sulfadiazine was remarkable, considering the age and the generally poor condition of the patient. It is thought that the action of sulfonamide compounds *in vivo* is bacteriostatic, rather than bactericidal, inhibiting the growth of organisms and allowing the phagocytes to engulf and destroy them. It is impressive, then, to observe such a prompt recovery in this elderly, debilitated man with severe anemia and a white cell count of less than 1,000. The transfusions were undoubtedly of considerable aid in supplying the deficient blood elements. The other important factor, of course, is the patient's antibody response, and it will be shown later that this patient had a high titer of circulating antibodies.

The source of infection was probably the superficial ulcer on the left thigh, since there was no other obvious focus, and since group C organisms are occasionally isolated from human skin.<sup>2b</sup>

The rash, which was similar to that seen in scarlet fever, was of considerable interest. Cases of scarlet fever caused by group C organisms have been reported,<sup>2b</sup> suggesting that an erythrogenic toxin, similar to the erythrogenic toxin produced by streptococci of group A, is produced. Similar rashes have also been observed in cases of bacteremia caused by group G strains.<sup>6</sup> The relation between the erythrogenic toxins produced by the various groups has not been studied. The Schultz-Charlton test, using group A antiserum, might contribute valuable infor-

A good many of these were pustules. On the lateral aspect of the left thigh there was a superficial ulcer, about 1 cm in diameter, which had apparently been present for several days. In addition to these lesions, there was a generalized reddening of the skin over parts of the trunk and extremities which was similar to the rash seen in scarlet fever. Small hemorrhagic areas were also present beneath the skin of the extremities. There were slight tenderness and swelling in the region of the left parotid gland. The throat was slightly injected, and the tongue was dry. The chest was emphysematous but otherwise clear to percussion and auscultation. The heart was not enlarged, and no murmurs were heard. Examination of the abdomen yielded nothing remarkable. There were signs of moderately advanced peripheral arteriosclerosis. Generalized muscular tenderness was present most markedly in the calves. The results of the physical examination were otherwise irrelevant.

*Laboratory Examination*—Examination of the blood revealed a hemoglobin content of 9.2 Gm per hundred cubic centimeters (Sahli), a red cell count of 2,200,000 and a white cell count of 680, with a differential count of 27 per cent polymorphonuclear leukocytes, 64 per cent lymphocytes, 6 per cent eosinophils and 3 per cent monocytes. The red cells showed marked anisocytosis, poikilocytosis and polychromasia. Toxic granules were present in the polymorphonuclear leukocytes. The platelets numbered 40,000. The percentage of reticulocytes was 1. The hematocrit reading was 23. The sedimentation rate was 70 mm in thirty minutes. The

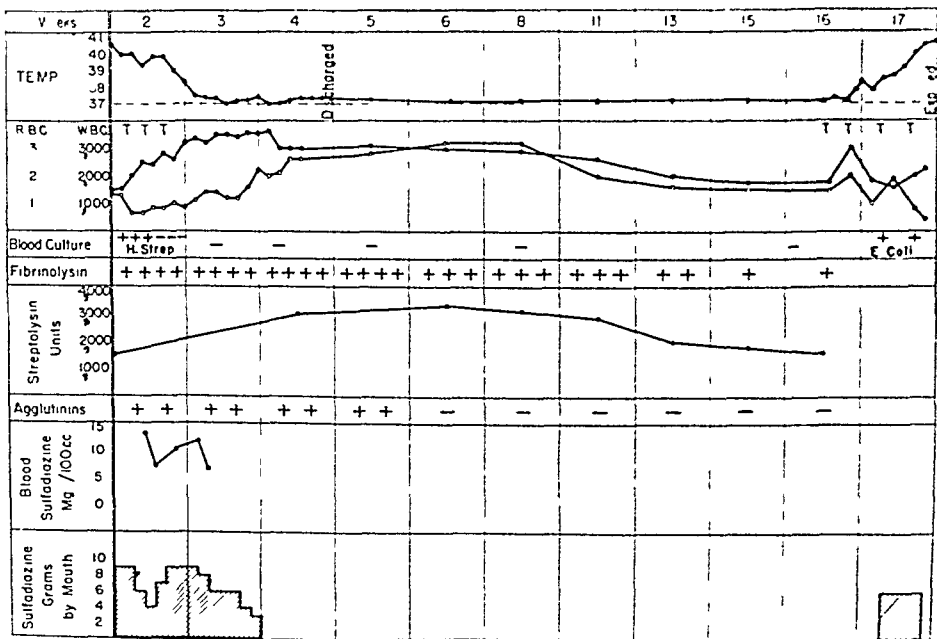


Fig 1—Clinical course of a patient with bacteremia caused by hemolytic streptococci of Lancefield group C

direct van den Bergh reaction was negative, and the indirect reaction was positive (0.64 units). The icterus index was 5. There was urobilinogen in the urine, the reaction for it being positive in a dilution of 1:128. The blood contained 5.4 mg of urea per hundred cubic centimeters. The stool and urine were normal, there was no Bence Jones protein in the urine. The Wassermann reaction was negative. A blood culture was positive for hemolytic streptococci, Lancefield group C, with six colonies per cubic centimeter.

*Diagnosis*—It was not clear at first whether the aplastic anemia was due entirely to the infection of the blood stream or whether the bacteremia was merely an intercurrent process developing during the course of some underlying disease. Sepsis was the immediate problem, however, and therapy was directed toward the eradication of the streptococcal infection.

*Course of Illness*—The important data are summarized in figure 1. Since the first chill occurred one week before entry, it is assumed that the bacteremia began at that time. Admission to the hospital, then, was during the second week of the illness.

Although the patient's prognosis seemed poor on admission, there was rapid improvement after therapy with sulfadiazine was begun. The blood culture was negative for hemolytic streptococci on the third day of hospitalization, the rash had disappeared and most of the pustules were beginning to heal within four days, and at the end of the eighth day the temperature was normal. Three blood transfusions were given during the first week. The remainder of the course of illness during the hospitalization was uneventful. Except for a

by hemolytic streptococci. Subsequent studies have shown that the test is not entirely specific for streptococcic infections, as increased amounts of antifibrinolysin have been noted in patients with gonococcic arthritis<sup>15</sup> bacteremia caused by *Streptococcus viridans*<sup>16</sup> and pneumococcic pneumonia.<sup>17</sup>

Fibrinolysin is produced by streptococci belonging to group A, group C human, and group G but not by organisms belonging to the other Lancefield groups.<sup>18</sup>

*Procedure and Results*—The organisms isolated from our patient were transferred daily to broth culture and antifibrinolysin tests were performed according to the method of Tillett and Garner,<sup>19</sup> except that the plasma-fibrinolysin solution was incubated for fifteen minutes before calcium chloride was added. Tests were

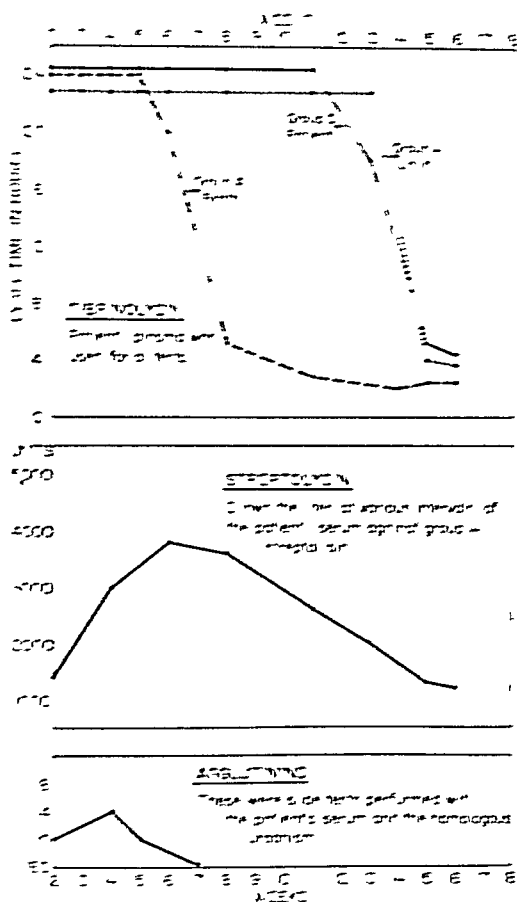


Fig. 3—A summary of the immunologic data in the case reported here.

also made with solid fibrinolytic substance prepared from a group A strain by the method of Garner and Tillett,<sup>19</sup> and with a broth culture of another group A strain.

15. Myers W. K., Keefe, C. S., and Holmes W. F., Jr.: The Resistance to Fibrinolytic Activity of the Hemolytic Streptococcus with Special Reference to Patients with Rheumatic Fever and Rheumatic (Atrophic) Arthritis. *J. Clin. Investigation* 14:119, 1935.

16. Wazler E.: Development of Antifibrinolytic Properties in Blood of Patients with Rheumatic Fever, Chronic Infective Arthritis and Bacterial Endocarditis. *J. Clin. Investigation* 16:145, 1937.

17. Boisvert P. L.: The Streptococcal Antifibrinolysin Test in Clinical Use. *J. Clin. Investigation* 19:65, 1940.

18. Tillett W. S.: The Fibrinolytic Activity of Hemolytic Streptococci. *Bact. Rev.* 2:161, 1935.

19. Garner R. L. and Tillett W. S.: Biochemical Studies on the Fibrinolytic Activity of Hemolytic Streptococci: I. Isolation and Characterization of Fibrinolysin. *J. Exper. Med.* 60:234, 1934.



mation, but unfortunately it was not done in this case. Further similarities in the properties of organisms of groups A, C and G organisms are to be presented and discussed later in this paper.

#### BACTERIOLOGIC DATA

The organisms were isolated from the patient's blood stream in dextrose infusion broth and on poured blood agar plates. On surface and on poured plates the colonies presented the typical appearance produced by organisms of Lancefield group C, which has been described by Rantz and Jewell<sup>13</sup>. Photographs of such plates are reproduced in figure 2. Surface and poured plates containing colonies of group A organisms are also included to show that their appearance differs from that of colonies of group C organisms. The chief difference lies in the size of the hemolytic zone, which is larger for group C strains and has a less distinct margin. The colony of group C organisms is somewhat larger, particularly on the poured plate.

The Lancefield grouping was performed by Rantz's modification of the formamide method of Fuller<sup>12a</sup>. The results were especially clearcut more so than is usually observed with group C organisms and there were no cross reactions.

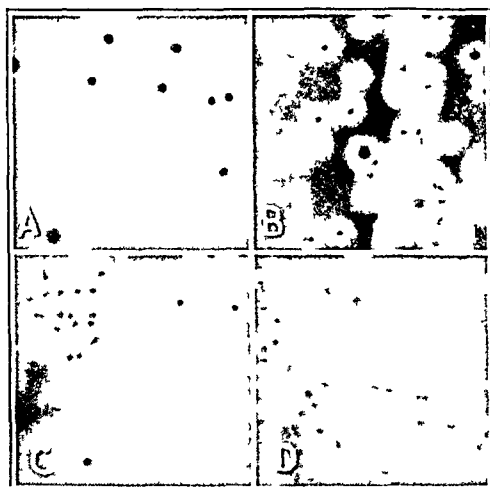


Fig 2—Poured (A) and surface (C) blood agar plates containing hemolytic streptococci of Lancefield group C isolated from our patient and similar preparations (B, poured plate; D, surface plate) of hemolytic streptococci of Lancefield group A. The colonies of group C organisms are larger than colonies of streptococci of group A, and the hemolytic zone is larger with a less distinct margin than that of the colonies of group A organisms.

After the organisms had been transferred in infusion broth daily for several weeks a small colony variant appeared. Its properties were studied but were not sufficiently different from the original large colony form to merit special mention.

#### FIBRINOLYSIN

Tillett and Garner<sup>14</sup> found in 1933 that broth cultures and cell-free culture filtrates of many strains of hemolytic streptococci of human origin contain a substance capable of dissolving clots of normal human fibrin and that a resistance to this lytic action develops in the plasma of patients during or after infections caused

13 Rantz, L. A., and Jewell, M. L. The Relationship of Serologic Groups A, B, and C of Lancefield to the Type of Hemolysis Produced by Streptococci in Poured Blood Agar Plates, *J. Bact.* **40** 1, 1940.

14 Tillett, W. S., and Garner, R. L. The Fibrinolytic Activity of Hemolytic Streptococci. *J. Exper. Med.* **58** 485, 1933.

streptolysin O is formed by strains belonging to groups A, C (human) and G but not by strains belonging to groups B, C (animal), D, E, G and K. It was inferred that the streptolysins O produced by groups A, C and G were identical. This observation is of special interest when it is recalled that A, C and G are the three groups that most commonly cause infections in human beings.

Streptolysin S, on the other hand, is group specific<sup>24</sup>, i. e., group A anti-streptolysin S does not neutralize the streptolysin S of any of the other groups.

The only description of titrations of antistreptolysin in human beings with infections caused by members of groups other than A is that of Longcope.<sup>8</sup> He found high titers of antistreptolysin O in 2 patients infected with the "minute hemolytic streptococci" of Long and Bliss,<sup>9</sup> which are members of group F. On the other hand, no streptolysin O was produced by the three group F strains studied by Todd<sup>21</sup> so that the status of the members of this group needs to be further studied.

Since antistreptolysin has not been prepared by injection of group C streptolysin into animals and since no previous studies have been reported on human subjects, it is of unusual interest to record the results of the experiments performed in connection with this patient.

*Comparison of Group A and Group C Streptolysin O*

	Group A	Group C
Minimal hemolytic dose		
Fresh culture	0.05 cc	0.05 cc
After filtration	0.05 cc	0.05 cc
After reduction	0.05 cc	0.10 cc
Combining unit with group A antistreptolysin	0.25 cc	0.3 cc
Titration with patient's serum on two occasions	1,075 units 1,000 units	2,500 units 3,000 units

*Procedure and Results*—Streptolysin O was prepared from group C organisms according to the method of Coburn and Pauli.<sup>25</sup> At the same time streptolysin O was made from a group A strain (Monson-Schuetzei). The data concerning the two lysins is presented in the table. Their behavior was almost identical in all respects. The group A lysin produced hemolysis somewhat more rapidly, but no difference could be detected after one half-hour's incubation. Neutralization was clearcut, and the combining unit was readily determined with group A anti-streptolysin. Of special interest were the titrations of the patient's serum with both group A and group C streptolysins. The patient's antistreptolysin titer against group A lysin is charted in figure 3, where it is correlated with the results of the agglutination and the fibrinolysin tests. A high titer developed early in the disease, and it was still considerably elevated at the time of the patient's death sixteen weeks later.

*Comment*—The streptolysins O of groups A and C are much alike. They are both actively lytic and are readily neutralized by both group A and group C antistreptolysin. The group C lysin is antigenic and produced a high titer of anti-streptolysin in the patient's serum. The titer was the same with group A and group C streptolysins, which suggests that no group specificity exists, but that the streptolysins produced by the two groups are similar if not identical.

25 Coburn, A. F., and Pauli, R. H. Studies on the Immune Response of the Rheumatic Subject and Its Relationship to Activity of the Rheumatic Process. I. The Determination of Antistreptolysin Titer, *J. Exper. Med.* **62**: 129, 1935.

The group C fibrinolysin was actively lytic, of almost the same potency as the solid group A substance. This similarity in action has been observed in over two hundred fibrinolysin tests. Comparative curves have been presented elsewhere.<sup>20</sup>

The patient's plasma was repeatedly tested against the fibrinolysin produced by the invading organism, as well as by the two group A strains. The results are presented in figure 3. Complete resistance to lysis developed for all three strains during the acute stage of the illness. The amount of antifibrinolysin began to decrease gradually after a few weeks at different rates for each of the strains.

*Comment*—There is a striking similarity in the action of the fibrinolysins produced by the group A and group C strains. Both are actively lytic and give almost identical results in normal persons and in persons with infections caused by organisms of group A. The titer of antifibrinolysin of the plasma of the patient with an infection caused by streptococci of group C is nearly the same when tested with group A and with group C lysins. If the fibrinolysins were group specific, there should have been a higher titer with the homologous than with the heterologous strains. As the titer fell however, there was actually a shorter fibrinolysin time with the group C (homologous) strain. It was shown by Mote, Massell and Jones<sup>21</sup> that there are quantitative differences in the fibrinolysins and antifibrinolysins produced by various group A strains. The differences in the group A and group C described in this paper are of the same nature. However, if there were actual qualitative differences the variations in titers should have been much wider than those recorded.

The evidence suggests that from a qualitative standpoint the fibrinolysins produced by group A and group C are similar, if not identical.

#### STREPTOLYSIN

It has been known for many years that hemolytic streptococci produce a soluble substance which is capable of lysing red blood cells. This substance, called streptolysin, is antigenic<sup>22</sup>; i. e., when it is injected into the blood stream of animals, it stimulates the production of a substance, antistreptolysin, which will neutralize the hemolytic activity of streptolysin *in vitro*. Increased amounts of antistreptolysin in human beings also develop during or after infections caused by hemolytic streptococci. Determination of the titer of antistreptolysin has become an important method for the study of known streptococcal infections and also of diseases of obscure origin, such as rheumatic fever and glomerulonephritis, which are thought to be associated in some way with hemolytic streptococci.

The relation between the streptolysins produced by members of the various Lancefield groups is a subject of considerable interest. Todd<sup>23</sup> found that two distinct serologic varieties of streptolysin can be prepared from hemolytic streptococci of group A. They have been named streptolysin O, to indicate sensitivity to oxygen, and streptolysin S, to indicate extractability in serum. It was later shown,<sup>24</sup> by neutralization experiments with group A antistreptolysin O, that

20 Kirby, W. M. M., and Rantz, L. A. The *in Vitro* and *in Vivo* Effect of Sulfonamides upon the Streptococcal Antifibrinolysin Test, *J. Clin. Investigation* **21** 295, 1942.

21 Mote, J. R., Massell, B. F., and Jones, T. D. Differences in Hemolytic Streptococcal Antifibrinolysins, *J. Immunol.* **36** 71, 1939.

22 Todd, E. W. A Comparative Serological Study of Streptolysins Derived from Human and from Animal Infections, with Notes on Pneumococcal Hemolysin, Tetanolysin, and Staphylococcus Toxin, *J. Path. & Bact.* **39** 299, 1934.

23 Todd, E. W. The Differentiation of Two Distinct Serological Varieties of Streptolysin, Streptolysin O and Streptolysin S, *J. Path. & Bact.* **47** 423, 1938.

24 Todd, E. W. The Streptolysins of Various Groups and Types of Hemolytic Streptococci. A Serological Investigation, *J. Hyg.* **39** 1, 1939.

three groups have been made, although it has been shown that erythrogenic toxin is not the same substance as streptolysin <sup>o</sup>. Groups A, C (human) and G strains all produce active fibrinolysins and streptolysins O, while strains belonging to the other groups do not.

The qualitative and quantitative relations between the streptolysins and the fibrinolysins produced by the three groups have been little studied, and most of the experiments have been performed with animals. Therefore the studies made in connection with our patient, which suggest that the fibrinolysins and streptolysins O of groups A and C are similar, if not identical, are particularly interesting.

It can be said that hemolytic streptococci of groups C and G have certain characteristics in common with members of group A and that they may be equally capable of producing severe infections in human beings. It is only through continued correlation of careful clinical and laboratory observations, such as have been attempted in this study, that the role of the various Lancefield groups of hemolytic streptococci in infections in human beings will be finally determined.

#### SUMMARY AND CONCLUSIONS

A case of bacteremia caused by hemolytic streptococci of Lancefield group C is reported in which recovery followed administration of sulfadiazine. Some clinical features of the case are discussed, including the mechanism of recovery and the nature of the scarlatiniform rash.

The pertinent literature is reviewed and the results of immunologic studies made in connection with this case are presented. The evidence suggests that the fibrinolysins and streptolysins O of groups A and C are similar, if not identical.

These findings are discussed in relation to the Lancefield groups as a whole, and it is pointed out that members of groups C and G have certain characteristics in common with members of group A and that they may be equally capable of producing severe infections in human beings.

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30 Todd E W, Laurent, L J M, and Hill, N G. An Examination of the Relationship Between Streptococcal Antitoxin and Antistreptolysin, *J Path & Bact* **36** 201, 1933.

## AGGLUTININS

Antibacterial immunity, the response of the body to the bacteria themselves rather than to their products, can be studied by demonstrating antibacterial agglutinins or precipitins in the blood serum. Agglutination tests, particularly with the tube method, are not entirely satisfactory in studying streptococcic infections, partly for technical reasons and partly because agglutinins seem to be formed irregularly.<sup>26</sup> The slide agglutination method introduced by Ozaki<sup>27</sup> has simplified the problem somewhat, particularly when a great many tests are being performed.

*Procedure and Results*—The results of slide agglutination tests performed with the homologous organisms are shown in figure 3. Agglutinins appeared in low dilution early in the illness and disappeared between the fifth and the seventh week after the onset of bacteremia. Tests performed against various Griffith types of group A organisms<sup>28</sup> were positive, undiluted, for types 2 and 25 throughout the entire period of sixteen weeks during which the patient was studied.

*Comment*—The results with the homologous organism are similar to those reported from other clinics<sup>29</sup> namely, that antibacterial immunity can be demonstrated for only a relatively short time after recovery from streptococcic infections. The positive reactions with types 2 and 25 of group A are of interest and indicate that some cross reactions do occur among the Lancefield groups.

## GENERAL COMMENT ON IMMUNOLOGIC DATA

Since 95 per cent of infections caused by hemolytic streptococci in human beings are caused by organisms belonging to group A (Lancefield) the opinion has become widespread that members of the other groups are relatively avirulent. Considerable clinical and experimental evidence is gradually accumulating, however, which suggests that this point of view may have to be modified. The evidence is largely made up of single, isolated observations which we have collected correlated with the case reported here and discussed in their relation to streptococcic infection in general.

Severe infections have been caused by members of groups other than A, chiefly groups C and G, suggesting that the frequency of infections due to organisms of the various groups may be partly a matter of general distribution of the organisms, rather than of relative virulence. Further, it is becoming apparent that organisms belonging to groups A, C and G have certain characteristics in common which are different from those of members of the other groups. These three groups are the ones most commonly isolated, in the order named, in infections in human beings, and this may be in part due to their unique properties. A characteristic rash, resembling that of scarlet fever, has been observed in cases of infection due to organisms in each of these three groups, suggesting that they all produce an erythrogenic toxin. Scarlet fever has been caused by group C organisms, and both group C and group G strains have been responsible for erysipelas. No studies of the qualitative or quantitative nature of the toxins produced by members of the

26 Myers, W. K., and Keefer, C. S. Antistreptolysin Content of the Blood Serum in Rheumatic Fever and Rheumatoid Arthritis, *J. Clin. Investigation* **13** 155, 1934.

27 Ozaki, M. The Agglutinin Content of Placental Sera for Various Types of Group "A" Streptococci, *Kitasato Arch. Exper. Med.* **14** 314, 1937.

28 Griffith, F. Serological Classification of *Streptococcus Pyogenes*, *J. Hyg.* **34** 542, 1935.

29 Schlesinger, B., and Signy, A. G. Precipitin Reactions in the Blood of Rheumatic Patients Following Acute Throat Infections, *Quart. J. Med.* **2** 255, 1933. Coburn, A. F., and Paul, R. H. Studies on the Relationship of *Streptococcus Hemolyticus* to the Rheumatic Process. III. Observations on the Immunological Response of Rheumatic Subjects to Hemolytic *Streptococcus*, *J. Exper. Med.* **56** 651, 1932.

subsequently commented on. It was only after the isolation by Collip<sup>5</sup> of a potent extract of the parathyroid glands that the relationship between these diverse clinical conditions and abnormalities of the parathyroid glands was recognized. It was found that the histologic and chemical changes produced by parathyroid extract in the experimental animal were indeed very similar to the histologic and chemical changes observed in patients with tumors of these glands.

Certain things then became clear. The common denominators in the apparently unrelated conditions of chronic renal disease, osteomalacia, rickets, carcinomatous metastasis to the bones<sup>6</sup> and osteitis fibrosa cystica were the extensive bony changes, although these changes were dissimilar in the various conditions, and the abnormalities of the parathyroid glands although these abnormalities also were different. One phenomenon, however, had been almost consistently observed and that was that when the bony changes were such as were described by Recklinghausen, a tumor of a parathyroid gland was almost always found, whereas in the other conditions all four parathyroid glands were usually hyperplastic.

The final crystallization of the pathologic distinction was provided by the work of Castleman and Mallory.<sup>7</sup> Employing their findings as a basis, they classified enlargements of the parathyroid glands into two groups—those due to tumor and those due to hyperplasia. Tumor usually affects one, rarely two parathyroid glands, the remaining parathyroid glands are perfectly normal grossly and histologically. When the pathologic enlargement of the parathyroid glands is due to hyperplasia, all four glands are usually involved. The enlargements in the latter group are further divided into primary and secondary. The primary hyperplasia produces actual primary hyperparathyroidism as described by Albright,<sup>8</sup> and the secondary, the hyperplasia which is usually associated with the presence of chronic renal disease, rickets, osteomalacia, multiple myeloma and Cushing's syndrome. The secondary hyperplasia occurs as a compensatory mechanism in response to the underlying disease. Perhaps it is worth while emphasizing that secondary hyperparathyroidism is a true hyperfunction of the parathyroid glands, although not amenable to therapy as is primary hyperparathyroidism.

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5 Collip, J. B. *The Parathyroids*, *Medicine* **5** 1, 1926.

6 Klemperer, P. *Parathyroid Hyperplasia and Bone Destruction in Generalized Carcinomatosis*, *Surg., Gynec. & Obst.* **36** 11, 1923.

7 Castleman, B., and Mallory, T. B. *Pathology of the Parathyroid Glands in Hyperparathyroidism. Study of Twenty-Five Cases*, *Am. J. Path.* **11** 1, 1935.

8 Albright, F. *Hyperparathyroidism Due to Idiopathic Hypertrophy of Parathyroid Tissue. Follow-Up Report on Six Cases*, *Tr. A. Am. Physicians* **52** 171, 1937.

# PRIMARY AND SECONDARY HYPERPARATHYROIDISM

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## GENERAL CONSIDERATIONS

In 1891 Recklinghausen<sup>1a</sup> described a curious disease of bone characterized by destruction and repair, marked softening of the bones and the presence of odd cysts. He recognized the similarity of his cases to that described by Engel<sup>1b</sup> some twenty-seven years previously. Recklinghausen was not aware of any endocrine disorder associated with the bony changes which he described. As a matter of fact during the course of the next number of years many pathologists noted tumors of the parathyroid glands in the presence of certain kinds of bone disease but failed to grasp the etiologic relationship between the two. Erdheim<sup>2</sup> was probably the first to recognize more than a casual relationship between the bony changes and the hyperplasia of the parathyroid glands in cases of osteomalacia, although his explanation of the observed phenomena later proved to be inadequate. It is easy to understand the early confusion of the pathologists. Hyperplasia of these glands had been observed in a variety of conditions. Thus MacCallum,<sup>3</sup> as early as 1905, reported enlargement of the parathyroid glands in chronic renal disease. Its presence in osteomalacia, rickets and Recklinghausen's disease was

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1 (a) von Recklinghausen, F, in Festschrift Rudolf Virchow zu seinen 71 Geburtstage, gewidmet von den fruheren und jetzigen Assistenten des Berliner pathologischen Instituts, Berlin, G Reimer, 1891. (b) Engel, G. Ein Fall von zystoidei Entartung des ganzen Skeletts, Inaug Dissert, Giessen, F C Pietsch, 1864

2 Dawson, J W, and Struthers, J W. Generalized Osteitis Fibrosa with Parathyroid Tumor and Metastatic Calcification, Including a Critical Discussion of the Pathologic Processes Underlying Osseous Dystrophies, Edinburgh M J 30 421, 1923

3 Erdheim, J, cited by Biedl A. Innere Sekretion, ed 2 Berlin, Urban & Schwarzenberg, 1913, pt 1, p 108

4 MacCallum, W G. Tumor of the Parathyroid Glands, Bull Johns Hopkins Hosp 16 87, 1905

in the calcium and phosphorus in the urine and decalcification of the bones. The marked increase in the calcium excreted in the urine can be utilized as a test for hyperfunction of the parathyroid glands, since the patient will excrete more calcium than he consumes and will be in negative calcium balance. The question as to whether there also occurs an increase in the calcium excreted in the stool in primary hyperparathyroidism is an interesting one. Albright and his co-workers<sup>11</sup> found that parathyroid extract exercised no effect on the fecal excretion of calcium in 8 patients: 4 with otosclerosis, 2 with chronic lead poisoning and 2 with ossifying hematomas. Bulger, Dixon and Barr<sup>15</sup> however, in their classic paper on hyperparathyroidism, found that in 2 of their 3 cases there did occur an increase in the fecal excretion of calcium. The essential difference between the two groups is that one dealt with persons in whom the parathyroid glands were not directly implicated, the other with patients in whom there was definite hyperfunction of these glands. The site of the excretion of calcium is determined to a great extent by the availability of a particular route for the excretion of calcium. The factors which may determine this will be discussed in greater detail later. But if for one or a number of different reasons, the amount of calcium which can be excreted in the urine is not adequate, as it may not be in chronic renal disease,<sup>16</sup> then an increase in the excretion of calcium and phosphorus into the gastrointestinal tract may result.

As was mentioned before the causative agent of osteitis fibrosa cystica or primary hyperparathyroidism is usually an adenoma of a parathyroid gland. Occasionally there may be an adenoma of more than one parathyroid gland.<sup>17</sup> However, Albright and his co-workers<sup>8</sup> described 6 cases of primary hyperparathyroidism associated with hypertrophy of the parathyroid glands in the absence of an actual tumor. Wilder<sup>18</sup> cited a case described by Dubois, Aub, Bauer and Richardson in which a patient presented all the classic signs and symptoms of hyperparathyroidism, including a negative urinary calcium balance. At opera-

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15 Bulger, H. A., Dixon, H. A., and Barr, D. P. The Functional Pathology of Hyperparathyroidism, *J. Clin. Investigation* **9** 143, 1931.

16 (a) Halverson, J. O., Mohler, H. K., and Bergem, O. The Calcium Content of the Blood Serum in Certain Pathological Conditions, *J. Biol. Chem.* **32** 171, 1927. (b) Sriver, W. de M. Observations on the Excretion of Calcium in Two Cases of Nephrosis Treated with Parathyroid Extract, *J. Clin. Investigation* **6** 115, 1928. (c) Hetenyi, G., and Nograde, S. V. Ueber die Kalkausscheidung der gesunden und kranken Niere, *Klin. Wchnschr.* **6** 1308, 1925.

17 Jaffe, H. L. Hyperparathyroidism, *Bull. New York Acad. Med.* **16** 291 (May) 1940.

18 Wilder, R. M. Hyperparathyroidism. Tumor of the Parathyroid Glands Associated with Osteitis Fibrosa, *Endocrinology* **13** 231 (May) 1929.



The use of a potent parathyroid extract <sup>9</sup> served to demonstrate the characteristic chemical changes which occur in hyperparathyroidism and which result in the classic bony changes. Greenwald and Gross <sup>9</sup> showed that the administration of parathyroid extract to dogs produced hypercalcemia with increased excretion of both calcium and phosphorus in the urine. The clinical picture of primary hyperparathyroidism then came into sharper focus and in 1926 Mandl <sup>10</sup> utilizing this information operated on a patient with osteitis fibrosa cystica and found and removed an adenoma of the parathyroid glands. The brilliant clinical recovery which followed this operation was a temporary one, but it served to establish the entity of osteitis fibrosa cystica associated with tumor of the parathyroid glands on a firm clinical footing. Mandl in this patient demonstrated essentially the same phenomena that Greenwald and Gross found in their dogs. Before operation the urine showed excessive amounts of calcium while after operation the calcium content fell to normal. In 1929 Albright and his co-workers <sup>11</sup> showed that the effects of parathyroid extract injected into man were similar to those in the dog. Somewhat earlier Hueper <sup>12</sup> demonstrated that metastatic calcification occurred characteristically in the lungs, the gastric mucosa and the kidneys after the administration of excessive amounts of parathyroid extract to dogs. Bauer and his group <sup>13</sup> and Jaffe <sup>14</sup> reported decalcification of the skeleton resulting from long-continued administration of parathyroid extract.

If we were to summarize the clinical findings of primary hyperparathyroidism we should find that they are essentially the same as those which follow prolonged administration of a parathyroid extract to dogs. There occur hypercalcemia, lowering of blood phosphate, increase

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9 Greenwald, I, and Gross, I. The Effect of Thyroparathyroidectomy in Dogs upon the Excretion of Calcium, Phosphorus and Magnesium, *J Biol Chem* **66** 185, 1925, The Effect of the Administration of a Potent Parathyroid Extract upon the Excretion of Nitrogen, Phosphorus, Calcium and Magnesium, with Some Remarks on the Solubility of Calcium Phosphate in Serum and the Pathogenesis of Tetany, *ibid* **66** 217, 1925.

10 Mandl, G. Klinisches und Experimentelles zur Frage der lokalisierten und generalisierten Ostitis fibrosa, *Arch f klin Chir* **143** 245, 1926.

11 Albright, F, Bauer, W, Ropes, W, and Aub, J. Studies in Calcium and Phosphorus Metabolism. IV. The Effects of the Parathyroid Hormone, *J Clin Investigation* **7** 139, 1929.

12 Hueper, W. Metastatic Calcifications in the Organs of the Dog After Injections of Parathyroid Extract, *Arch Path* **3** 14 (Jan) 1927.

13 Bauer, W, Aub, J C, and Albright, F. Studies of Calcium and Phosphorus Metabolism. V. A Study of the Bone Trabeculae as a Readily Available Reserve Supply of Calcium, *J Exptl Med* **19** 145, 1929.

14 Jaffe, H L. Hyperparathyroidism, *Arch Path* **16** 63 (July), 236 (Aug) 1933.

tion between primary hyperparathyroidism and chronic renal disease with secondary hyperparathyroidism is frequently quite difficult. It must be remembered that in Recklinghausen's disease recurrent renal calculi may occur, which can produce extensive renal damage. In these instances chronic renal failure may develop, which may produce a distortion of the characteristic chemical findings in the blood. One sees the combination of a well defined adenoma of a parathyroid gland with hyperplasia of the remaining parathyroid glands. Such a case was described by Downs and Scott<sup>25</sup> and such an instance is included in our group (case 3). In these cases it is possible to postulate that the chronic renal failure resulting from the adenoma of the parathyroid gland has induced in turn, hyperplasia of the other parathyroid glands.

The question arises as to why hyperplasia of the parathyroid glands develops in patients with chronic renal insufficiency. We know that the chronic renal disease and the chronic acidosis precede the glandular hyperplasia. Bony changes, notably decalcification,<sup>26</sup> have been described in chronic renal failure, while acidosis is not infrequently associated with increase in the urinary calcium output.<sup>15</sup> Perhaps the increase in the urinary excretion of calcium under such circumstances occurs because the ability of the kidneys to form ammonia is impaired. In any event, while calcium is excreted in the urine in excessive or in adequate amounts, phosphate is retained. It is a moot point whether the parathyroid glands are concerned primarily with the metabolism of calcium or with that of phosphorus. Since the two ions enjoy a reciprocal relationship expressed essentially by the equation  $[Ca^{++}]^3 \times [PO_4^{==}]^2 = K$ , it is questionable whether one can distinguish a primary effect on either of these ions. However, Albright and his co-workers<sup>11</sup> expressed the opinion that the primary effect of parathyroid extract is on the metabolism of phosphorus rather than on that of calcium. This apparently was the view of Shelling and Remsen, too.<sup>22</sup> Albright contended that parathyroid extract causes primarily an increase in the urinary excretion of phosphorus with resulting hypophosphatemia. Because of the lowered level of serum phosphorus, the serum is less saturated with calcium phosphate, and consequently there is an increased tendency for calcium phosphate to enter the blood, either from the bones or from the gastrointestinal tract. This produces hypercalcemia and secondarily hypercalciuria.

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25 Downs, R. S., and Scott, V. Hyperparathyroidism with Adenoma Causing Renal Failure and Secondary Hyperparathyroidism, *Arch. Int. Med.* **67**: 658 (March) 1941.

26 Ginzler, A. M., and Jaffe, H. L. Osseous Findings in Chronic Renal Insufficiency in Adults, *Am. J. Path.* **17**: 292, 1941.

tion, however, no abnormalities were found. Two normal parathyroid glands were removed, and this was followed by a considerable improvement in the patient's condition. Wilder concluded that there can be hyperfunction of the parathyroid glands without either hypertrophy or tumor, and he drew an apt analogy to the hyperinsulinism occurring in the absence of an adenoma involving the islets of Langerhans. That this is a distinct possibility may well be true. But it should be remembered that a tumor may be present in an aberrant parathyroid gland located in the mediastinum and if not specifically and expertly looked for, it may very well be missed (note cases 1 and 2).

Patients with secondary hyperparathyroidism form a relatively large group, and one never finds an isolated adenoma of a parathyroid gland in these patients but, rather, hyperplastic glands with or without the characteristic bony and chemical changes, or the bony and chemical changes with histologically perfectly normal parathyroid glands. Secondary hyperparathyroidism may occur in patients with chronic renal disease, multiple myeloma, carcinomatous metastasis to the bones, Cushing's syndrome, rickets, osteomalacia and perhaps several other clinical conditions. The most common of these is chronic renal disease.

Bergstrand,<sup>19</sup> Hubbard and Wentworth,<sup>20</sup> Pappenheimer and Wilens,<sup>21</sup> Shelling and Remsen,<sup>22</sup> Shelling,<sup>23</sup> and Anderson<sup>24</sup> have reported excellent studies on the relation of chronic renal disease to hyperparathyroidism. The characteristic picture is that observed in a patient with long-standing renal disease and chronic acidosis in whom extensive bony changes have developed. The blood calcium is usually normal but may be either depressed or elevated. The blood phosphorus, however, is almost always elevated. Studies of the calcium balance usually yield results similar to those obtained in a patient with primary hyperparathyroidism. Roentgenographic studies of the skeleton generally show extensive decalcification of bony structures and not infrequently metastatic calcification in various other parts of the body. The parathyroid glands may be markedly hyperplastic. The clinical distinc-

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19 Bergstrand, H. Parathyroideastudien. II. Ueber Tumoren und hyperplastische Zustände der Nebenschilddrüsen, *Acta med Scandinav* **54** 539, 1921.

20 Hubbard, R. S., and Wentworth, J. A. A Case of Metastatic Calcification Associated with Chronic Nephritis and Hyperplasia of the Parathyroids, *Proc Soc Exper Biol & Med* **18** 307, 1921.

21 Pappenheimer, A. M., and Wilens, S. L. Enlargement of the Parathyroid Glands in Renal Disease, *Am J Path* **11** 73, 1935.

22 Shelling, D. H., and Remsen, D. Renal Rickets, *Bull Johns Hopkins Hosp* **57** 158, 1935.

23 Shelling, D. H. The Parathyroids in Health and Disease, St. Louis, C. V. Mosby Company, 1935.

24 Anderson, W. A. D. Hyperparathyroidism and Renal Disease, *Arch Path* **27** 753 (April) 1939.

there may be a disturbance in this relationship. This will happen particularly in the presence of extensive renal disease. In the absence of such renal disease the elevation of the blood calcium is compensated for by increased excretion of phosphorus in the urine above that of calcium so that the product of the calcium and the phosphorus concentration remains constant. When renal failure occurs, however, and the urinary excretion of phosphorus is reduced the relationship between the calcium and the phosphate ions is altered, both in the urine and in the blood. In addition the other factors which govern the solubility of the calcium are also changed. As a result, the degree of solubility of calcium phosphate is changed in these mediums. Such alterations in the factors governing the solubility of the calcium probably determine precipitation of calcium phosphate in the tissues. In this respect it is interesting to note that deposits of calcium occur particularly in the lungs, the gastric mucosa and the kidneys—organs in which the hydrogen ion concentration may vary considerably from that of the blood.

#### CLINICAL CONSIDERATIONS

The symptoms of primary hyperparathyroidism may be roughly divided into two large groups—the general symptoms, such as weakness, lassitude, anorexia, loss of weight, diffuse aches and pains and others, and the specific symptoms—that is, those referable to the genitourinary tract, the skeletal system and the hypercalcemia. The genitourinary symptoms are those associated with recurrent renal calculi. Probably 30 to 40 per cent of the patients with primary hyperparathyroidism have evidence of the presence of urinary calculi at some time or other during the course of the disease. Not infrequently the first evidence of the illness is the presence of such stones. Of 17 cases presented by Albright and his group<sup>29</sup> 8 were discovered during routine determinations of the blood calcium in patients with urinary lithiasis. In 3 of the 5 cases included in our group of Recklinghausen's disease urinary calculi were found. Such stones may appear years before any other signs of hyperparathyroidism are present. Not infrequently, the calculi are bilateral. The evidence of progressive renal failure so often seen in patients with primary hyperparathyroidism occurs in these patients with renal calculi. Deposition of calcium may also occur in the renal substance itself.

In instances in which renal calculi have produced impairment of renal function, there may occur a distortion of the characteristic chemical findings in the blood usually seen in Recklinghausen's disease. In these instances the blood phosphorus may be elevated and the urinary calcium

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29 Albright, F., Aub, J. C., and Bauer, W. Hyperparathyroidism. Common and Polymorphic Condition as Illustrated by Seventeen Proved Cases from One Clinic, *J. A. M. A.* **102** 1276 (April 21) 1934.

The proponents<sup>27</sup> of the other theory held that parathyroid extract acts on bone tissue to dissolve and liberate calcium phosphate. This causes hypercalcemia, hypercalciuria and hyperphosphaturia. But, as Albright rightly pointed out, some secondary mechanism is required to explain the hypophosphatemia.

It would be pointless for us to become involved in a review of the extensive arguments and experimental evidence which have accumulated concerning these two hypotheses. Clinically, we shall assume that the parathyroid glands are concerned with the metabolism of calcium and phosphorus, particularly with the mechanism of the excretion of these ions.

Occasionally one finds instances of both renal rickets and primary hyperparathyroidism in which the excretion of calcium in the urine is reduced. In these instances studies of the calcium balance performed on the urine will not yield the characteristic results. Snapper<sup>28</sup> attempted to explain this on the basis of vitamin D deficiency. S. H. Liu and his co-workers, quoted by Snapper<sup>28</sup> found that in vitamin D deficiency urinary excretion of calcium is diminished, although the blood calcium may be normal or even elevated. This explanation however, probably does not hold for the patients with hyperparathyroidism seen in this country. The reduced urinary excretion of calcium occurs only in instances in which there is present extensive renal damage and it is the latter factor which probably determines the reduction of the urinary calcium output. This hypothesis received experimental confirmation in the work of Halverson and his co-workers<sup>14a</sup> that of Scriver<sup>16b</sup> and that of Hetenyi and Nograd<sup>16c</sup>.

One of the interesting phenomena occasionally observed both in primary hyperparathyroidism complicated by renal impairment and in secondary hyperparathyroidism due to renal disease is that of diffuse metastatic calcification. The presence of metastatic calcific deposits represents precipitation of calcium phosphate. The solubility of calcium phosphate is made possible and is also limited by certain physicochemical relationships, such as the  $p_H$  of the solvent medium, the carbon dioxide tension, the protein concentration and finally the total electrolyte concentration of the medium. These factors which determine the degree of solubility of calcium phosphate in the serum also determine its solubility in other mediums, such as the urine and perhaps the tissues. When the factors mentioned are kept constant the solubility of calcium phosphate is constant, that is  $[Ca^{++}]^3 \times [PO_4^{=}]^2 = K$ . In hyperparathyroidism

27 Thompson, D. L., and Collip, J. B. The Parathyroid Glands, *Physiol. Rev.* **12** 309, 1932. Jaffe<sup>14</sup>

28 Snapper, I. Different Features of the Syndrome of Hyperparathyroidism, *Acta med. Scandinav.* **103** 321, 1940.

In exploring for the presence of an adenoma of the parathyroid glands, it should be remembered that one or more of these glands may be aberrant and may be located in the superior mediastinum. No surgical exploration is complete unless all four of the glands have been visualized. Although, generally speaking, only one gland is adenomatous, occasionally more may be involved.

Following parathyroidectomy, there will occur a prompt drop in the blood calcium, so that within twenty-four hours it may have returned to normal or even fallen to tetanic levels. The blood phosphorus does not increase for several days, while the blood phosphatase may stay elevated for many months or even years.<sup>30</sup>

The onset of tetany after operation is not uncommon and may occur at any time within the first two weeks. When tetany occurs within the first twenty-four hours, it is not infrequently associated with a normal level of blood calcium but a level which is considerably lower than that present preoperatively. Tetany which appears after several days is always associated with blood calcium values which are at tetanic levels. The postoperative tetany may be due to one of several factors. The most important perhaps is functional atrophy of the normal parathyroid glands. After removal of the tumor, the remaining parathyroid glands will in time resume their normal function, but until such time tetany may appear and supportive treatment be indicated. Another common cause of postoperative tetany is the removal of too much parathyroid tissue. This usually occurs in those instances in which more than one exploratory operation has been performed before a tumor is found and removed, normal parathyroid glands being removed in the preliminary operations. The tetany which results in these instances is of a permanent character. Finally, tetany may follow a precipitate postoperative drop in the blood calcium. The tetanic manifestations may appear despite the fact that the blood calcium value is practically normal.

The treatment of postoperative tetany is essentially the same as that of spontaneous tetany. Calcium is administered by mouth and parenterally, the chloride and gluconate being used intravenously. The latter may be used intramuscularly and subcutaneously. The mild tetanic manifestations are readily controlled with the aid of calcium alone, particularly when this is given intramuscularly or intravenously. The more severe manifestations, however, require in addition the use of solution of parathyroid or of dihydrotachysterol. Solution of parathyroid<sup>30a</sup>

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30 Gutman, A. B., Tyson, T. L., and Gutman, E. B. Serum Calcium, Inorganic Phosphorus, and Phosphatase Activity in Hyperparathyroidism, Paget's Disease, Multiple Myeloma and Neoplastic Disease of the Bones, *Arch. Int. Med.* **57**: 379 (Feb.) 1936.

30a The preparation used in the cases reported was one meeting the standards for solution of parathyroid U. S. P.

reduced. This group is particularly difficult to distinguish from instances of renal rickets, and the most helpful aid in the differentiation lies in eliciting a careful history of the onset of the disease. The prognosis in this group is usually poor despite the successful removal of an adenoma of a parathyroid gland, since the patient may succumb to progressive renal failure. It is imperative to diagnose primary hyperparathyroidism before irreversible changes in the kidneys have occurred.

The skeletal changes in primary hyperparathyroidism may be manifested by spontaneous fractures, lumps, usually of the extremities, the ribs and the clavicles, and soft tumors of the jaw diagnosed as epulides. There may be marked deformities and a considerable reduction in height of the patient, and in extreme involvement, distortion of the bones in all directions. Patients with the disease in this form are less commonly seen today, probably because physicians are more aware of the possibility of hyperparathyroidism, and the disease is therefore recognized earlier. Pathologically, the most outstanding change in the bones is the generalized demineralization. Later there occur cysts, giant cell tumors, osteoclasts and osteoblasts and large deposits of fibrous tissue. In this disease, then, resorptive and reparative processes go on simultaneously, so that in place of the original bone and marrow spaces there are present fibrous tissue, abundance of osteoclasts and osteoblasts and some new bone. The destruction of bone, however, exceeds the formation of new bone. Roentgenologically, the decalcification and the cyst formation are easily evident, and usually the entire skeleton is involved in one way or another to varying degrees. In simple neoplastic metastasis to bones there are areas which appear entirely normal in roentgenograms in contrast with the metastatically involved areas. This lack of universal involvement in the latter condition helps to distinguish roentgenologically between the two.

The symptoms usually associated with the hypercalcemia of primary hyperparathyroidism are polyuria, polydipsia, muscular atony, bradycardia and occasionally cardiac irregularities.

The characteristic metabolic chemical changes consist of hypercalcemia, hypophosphatemia, hypercalciuria, hyperphosphaturia and a considerable increase in the blood phosphatase. In addition, the patients usually have a negative urinary calcium balance, that is the excretion of calcium is considerably in excess of the intake.

It must be remembered that the chemical findings just enumerated need not, and indeed do not, occur in all cases. This is particularly true in the presence of impaired renal function.

The treatment of primary hyperparathyroidism is always surgical. When the renal damage and the skeletal changes are not too extensive, the ultimate outlook for the patient is good. Recalcification of the bones will eventually occur although the cysts will remain essentially unaffected.

The patient was admitted to the hospital for the third time in November 1939, complaining of pain in the left flank, weakness and hematuria of three weeks' duration. On physical examination, it was found that her blood pressure had increased to 190 systolic and 100 diastolic and that she had definite masses in both flanks. Roentgenograms of the kidneys showed bilateral renal calculi, while roentgenograms of the skeletal structure showed irregular absorption of the trabeculae of the long bones, areas of rarefaction and increased density in the skull, cyst formation in the ribs and calcification of the pelvic vessels. The blood calcium now varied from 10.4 to 11.9 mg and the phosphorus from 4.5 to 5.6 mg per hundred cubic centimeters. The blood phosphatase was 44 King-Armstrong units and the urea nitrogen varied from 28 to 60 mg per hundred cubic centimeters.

The possibility of a parathyroid tumor was now seriously entertained, but surgical exploration of the neck failed to reveal any abnormal parathyroid glands, although only three were visualized.

The patient was again admitted to the hospital in August 1940, because of a fracture of the neck of the right femur. The blood calcium now varied from 11.0 to 13.0 mg and the phosphorus from 4.0 to 8.4 mg per hundred cubic centimeters. The blood phosphatase varied from 22 to 82 King-Armstrong units, and the urea nitrogen constantly mounted. Several months after this final admission the patient died in uremia.

On postmortem examination an adenoma of a retrosternal parathyroid gland was found, which weighed 12 Gm.

*Comment*—There are several points which stand out sharply in this case. They are the duration of the illness, which was approximately nine years, the predominant renal clinical picture with the formation of calculi, the observation that the blood calcium, although elevated, was not unduly so, while the phosphorus, even in the early stages of the disease, was not strikingly low, and the exploratory operation which failed to reveal the adenoma because the involved gland was retrosternal. When renal failure became well advanced, it was impossible to determine whether the hyperparathyroidism was primary or secondary to the disease of the kidneys. The discovery of an adenomatous parathyroid gland, in addition to the three normal glands, and the calculous character of the renal disease on postmortem examination finally revealed this case to be one of true primary hyperparathyroidism.

CASE 2—I V, a white woman 34 years of age, was admitted to the hospital in February 1934, complaining of urinary incontinence and diurnal and nocturnal frequency of four months' duration. Two years previously she had had similar symptoms, which were corrected after anterior and posterior colporrhaphy. During the present stay in the hospital, roentgen studies of the pelvis showed coarsening of the trabeculae of the innominate bones and of the head of the femur, as well as areas of increased density and smaller areas of transparency. These roentgen findings were interpreted as suggesting Paget's disease, although the blood calcium varied between 11.9 and 13.8 mg and the phosphorus between 3.0 and 3.1 mg per hundred cubic centimeters. The blood phosphatase was 70 King-Armstrong units.

The patient was readmitted to the hospital seven months later because of recurrent attacks of pain in the right side of the chest anteriorly, of sixteen days' duration. On examination, it was found that she had asymmetry and tremors of the tongue, hyperalgesia of the left side of the back corresponding to dorsal segments 7 to 10, marked tenderness over the middorsal region of the spinal column and a stocking type of hypoalgesia of the entire left leg. Roentgenologi-



may be given intravenously or subcutaneously, dihydrotachysterol, however, may be used orally only. The dose of solution of parathyroid varies with the intensity of the symptoms. Although usually a dose yielding 10 to 20 parathyroid units several times a day is adequate, much larger doses may be given with safety. Dihydrotachysterol is given in doses of 1 to 2 cc. of a 0.5 per cent solution in oil three times a day during the period of severe tetany. The danger of overdosage with either of these products lies in the development and persistence of hypercalcemia, with increase in the urinary excretion of calcium and phosphorus.

The postoperative treatment of hyperparathyroidism other than the treatment of tetany is important. Large amounts of calcium are required for remineralization of the bones and the patients show a remarkable avidity for calcium. This is well shown in a case in the series reported by Bulgei, Dixon and Barr<sup>15</sup> in which 350 Gm. of calcium and 180 Gm. of phosphorus were stored over a period of approximately ten months. Calcium thus stored is probably used for recalcification of the skeleton. Consequently it is important to give the patients daily supplementary amounts of calcium by mouth in addition to that which they normally consume in their diets. In this respect, it is important to remember to avoid an excessive intake of phosphate. With such an intake calcium will be used to precipitate the excess phosphate as calcium phosphate into the large bowel.

In addition to the daily 3 to 5 Gm. of a calcium salt it is desirable to give small amounts of vitamin D. The latter increases the absorption of calcium from the intestinal tract and helps to divert the calcium to the bones. An excess of vitamin D, however, should be avoided since parathyroid hypoplasia may result.

#### REPORT OF CASES

##### *Cases of Primary Hyperparathyroidism*

CASE 1—B. K., a white woman 47 years of age, was admitted to the hospital for the first time in November 1932. At that time she complained of pain in the lower part of the back, dysuria, diurnal and nocturnal urinary frequency, fatigue and weakness of ten days' duration. Ten years prior to this she had similar complaints, which subsided after several days. On investigation in the hospital, the only positive findings were a palpable left kidney, blood urea nitrogen amounting to 20 mg. per hundred cubic centimeters and blood pressure varying from 160 systolic and 90 diastolic to 170 systolic and 100 diastolic. Unfortunately the blood calcium and phosphorus were not determined at that time.

The patient was then lost sight of until 1934, when she was readmitted with acute bronchopneumonia. When she recovered from this her renal status was again investigated. Both kidneys were now palpable, and renal roentgenograms revealed bilateral dendritic calculi. There was marked impairment of renal function as measured by the phenolsulfonphthalein and urine concentration tests. The blood urea nitrogen amounted to 41 mg. per hundred cubic centimeters, while the blood calcium varied from 11.4 to 12.5 mg. and the blood phosphorus from 3.2 to 3.7 mg. per hundred cubic centimeters.

noticed a tumor of the left lower jaw. Five years prior to his admission to the hospital a calculus had been removed from the urinary bladder, and for the past two years he had had recurrent epulides.

On investigation in the hospital, it was found that he had a soft tumor of the left lower jaw. The blood calcium was 14.0 mg, while the phosphorus was 3.3 mg, per hundred cubic centimeters. The phosphatase was 53 King-Armstrong units. The blood urea nitrogen amounted to 29 mg per hundred cubic centimeters. A study of calcium balance yielded the following result. With a calcium intake of 100 mg daily over a three day period, the patient excreted 902 mg of calcium in the urine. Roentgen studies of the skeleton showed diffuse decalcification. Cysts were present in the left and right radii and ulnas, in the ischia, the left fibula, the right tibia and the right humerus.

It was evident on the basis both of clinical and laboratory studies that this patient had hyperparathyroidism. Consequently, on June 30, eight days after his admission to the hospital, he was operated on and four enlarged parathyroid glands were found, two of which (the left superior and the right inferior) were excised. Microscopic study of the removed glands showed the presence of a chief cell adenoma of one of them, with some hyperplasia of the oxyphilic and clear cells of the other.

Following the operation, the blood calcium fell progressively to 11.4 mg per hundred cubic centimeters, while the phosphorus remained essentially unchanged. Another study of the calcium balance just prior to his discharge from the hospital showed marked reduction in the excretion of calcium, so that with an intake of 300 mg of calcium over a three day period he now excreted only 495 mg. Studies of the urine during this period showed the specific gravity fixed at 1.012, with a trace of albumin, 2 to 4 red blood cells per high power field and occasional casts. The blood pressure was never elevated.

The patient was admitted to the hospital for the second time in October 1939, approximately fifteen months after the first admission. He continued to complain of weakness, fatigue and pains, particularly of the knees and the elbows. In addition, he had noticed a recurrence of the tumor of the jaw which had been previously removed. The blood calcium had again increased to 13.1 mg, while the blood phosphorus was 3.1 mg and the urea nitrogen was 13 mg per hundred cubic centimeters. The blood phosphatase was still elevated to 48 King-Armstrong units. The test for excretion of calcium showed only slight improvement over the previous result. Over a three day period he excreted a total of 417 mg of calcium in the urine following a total intake of 300 mg of calcium. Roentgenograms of the bony structure showed relatively little improvement since his last admission to the hospital. The renal function continued to show marked impairment. The specific gravity was still fixed at 1.012, and the urea clearance was 43 per cent of normal, while the phenolsulfonphthalein test showed 15 per cent excretion in four hours. It was decided to operate again, and the remaining right parathyroid gland and over one-half of the remaining left parathyroid gland were removed.

On October 30, eight days after the operation, the blood calcium had fallen to 9.2 mg, while the blood phosphorus had increased to 4.5 mg per hundred cubic centimeters. Approximately two weeks after the operation, tingling and quivering of the extremities developed. The deep reflexes were hyperactive. He had marked bilateral ankle clonus and a Chvostek sign. The blood calcium at this point was 5.6 mg, the phosphorus 4.8 mg and the urea nitrogen 30 mg per hundred cubic centimeters, and the carbon dioxide-combining power was 50.5 volumes per cent. It was evident that the patient had tetany. He was treated with calcium gluconate.

cally, there was compression of the third, fourth, fifth and eleventh dorsal vertebrae, the facial bones showed thickening and irregular mottling due to partial absorption of calcium, the skull showed changes suggestive of Paget's disease and the right femur now showed several cysts. The blood calcium varied between 12.2 and 13.4 mg, and the phosphorus had decreased to 2.2 mg per hundred cubic centimeters. The blood phosphatase was 47 King-Armstrong units.

In January 1936, one and one-half years after the last admission, the patient was readmitted to the hospital, complaining of headache, vomiting and pain in the epigastrium radiating to the back, of one week's duration. It was now found that her head had grown considerably larger and that considerable kyphosis of the upper dorsal part of the spinal column had developed, with slight scoliosis. The roentgen appearance of the skeleton was essentially as before, and roentgenologically it was impossible to determine whether the evident changes were due to hyperparathyroidism or to Paget's disease. On Feb. 11, 1936, a biopsy of the greater trochanter of the right femur was reported to have shown changes typical of osteitis fibrosa cystica. The blood calcium on this admission varied between 11.8 and 13.5 mg and the phosphorus between 2.6 and 3.3 mg per hundred cubic centimeters. The blood phosphate was 13.4 King-Armstrong units. A study of calcium balance was made for the first time during this period and showed a strongly negative calcium balance. With a total calcium intake over a three day period of 300 mg, she excreted 1,050 mg of calcium in the urine during this same period.

It was now evident that the patient had hyperparathyroidism. On Feb. 18, 1936, she was operated on, but no abnormal parathyroid glands were found.

In November 1938 she was reinvestigated. She had lost over 30 pounds (13.5 Kg) in weight since the last admission. There was a decrease in height of  $3\frac{1}{2}$  inches (8.9 cm). The left femur was bowed and thickened, as was the right ulna. The skull had increased markedly in size. The blood calcium was 12.0 mg and the phosphorus 2.9 mg per hundred cubic centimeters. The blood phosphatase was 140 King-Armstrong units. The result of a study of calcium balance was even more striking. With an intake of 300 mg over a three day period, she excreted 1,300 mg of urinary calcium. A second exploratory operation revealed a large adenoma of a parathyroid gland in the mediastinum. This was successfully removed.

The patient was seen in October 1939 and in April 1940. She felt quite well but had continued to decrease in height. Roentgen studies of the long bones and of the skull showed increased density in the previous areas of rarefaction but also gave considerable evidence suggestive of Paget's disease. The blood calcium amounted to 9.1 and 10.4 mg and the phosphorus 3.9 and 4.1 mg per hundred cubic centimeters. The blood phosphatase had fallen to 80 King-Armstrong units.

*Comment*—This case is of particular interest because it involved differentiation between Paget's disease and hyperparathyroidism. Generally speaking, with the aid of laboratory and roentgen findings the two conditions can be clearly distinguished. In this patient both conditions were apparently present, evidenced by the continued decrease in height and the increase in the size of the skull after a successful operation. This case is of further interest because of the mediastinal location of the adenomatous parathyroid gland.

**CASE 3**—E. P., a white man 42 years of age, was admitted to the hospital for the first time in June 1938. He complained of lassitude and fatigue and of anorexia of five years' duration. For several months prior to admission he had experienced pains "all over the body," and during the past two months he had

centimeters The blood phosphatase was 34 King-Armstrong units Tests of renal function gave essentially normal results, and the urea nitrogen amounted to 130 mg per hundred cubic centimeters Roentgen studies of the bony structure showed little change in the cystic formation in the left ilium and equivocal slight decalcification of the long bones On April 30 she was operated on and a tumor of the right inferior parathyroid gland was found The pathologic report revealed the tumor to be a chief cell adenoma Five days after operation, signs and symptoms of mild tetany developed The blood calcium at this time amounted to 8.5 mg per hundred cubic centimeters She responded promptly to solution of parathyroid and calcium, and after a few days this therapy could be discontinued

From the time of the operation until August 1939, when she was lost sight of, she continued to complain of diffuse aches and pains The blood calcium now varied from 9.2 to 9.8 mg and the phosphorus from 5.0 to 5.4 mg per hundred cubic centimeters The blood phosphatase was 15 King-Armstrong units Tests of renal function still gave normal results, and the blood urea nitrogen amounted to 14 mg per hundred cubic centimeters Intravenous pyelograms were fairly normal Roentgen studies of the skeletal system showed no essential change from the results of the previous investigation It must be emphasized, however, that at no time were the bony changes particularly striking

*Comment*—This case is of interest because the predominant findings were recurrent renal calculi The bony changes were always minimal, although the patient apparently had hyperparathyroidism for at least six years before operation

CASE 5—D F, a white woman aged 54, was admitted to the hospital in March 1939 She complained of generalized aches and pains of twenty-one years' duration, decrease in height of 2 inches (5 cm) during the past two years, loss of 40 pounds (18 Kg) during this period, inability to walk because of severe pains in the legs of eight months' duration, and polyuria and polydipsia for the past half year It is interesting that fifteen years before, on the basis of roentgen studies of the skull, she was suspected of having Paget's disease Seven years before, she was found to have hypertension (190 systolic and 100 diastolic) Two years before, she was investigated in a hospital in California During this study the blood calcium was found to be 8.5 mg, the phosphorus 4.2 mg and the urea nitrogen 38 mg per hundred cubic centimeters Roentgenograms of the skeleton showed diffuse osteoporosis She suffered from moderate secondary anemia, the hemoglobin being 55 per cent and the red blood cell count 3,400,000 The urine showed albumin and casts It was felt that she had chronic diffuse glomerular nephritis with secondary hyperfunction of the parathyroid glands

On her admission to the hospital in March 1939, roentgen studies of the bones showed two large cysts in the fifth and sixth ribs on the left side, spontaneous fracture of the fifth rib, fibrocystic changes of the left ilium and osteoporosis of the dorsal part of the spinal column, the skull, the pelvis and the femur The blood calcium was found to be 13.5 and 13.2 mg and the phosphorus 3.6 and 3.8 mg per hundred cubic centimeters The urea nitrogen amounted to 38 mg per hundred cubic centimeters and the blood phosphatase to 76 King-Armstrong units The blood pressure was 130 systolic and 80 diastolic, and the test of urine concentration showed inability to concentrate above 1.014 and fixation of the specific gravity between 1.010 and 1.014 The urine showed a small amount of albumin and an occasional cast

Because of the elevation of the blood calcium in the presence of chronic renal disease, it was felt that this patient had primary hyperparathyroidism An explora-

intravenously and given a low phosphorus, high calcium diet and dihydrotachysterol. Improvement was fairly prompt, although not striking in extent. The blood calcium increased to 8.3 mg and the phosphorus dropped to 3.6 mg per hundred cubic centimeters. He was discharged from the hospital for ambulatory treatment. Microscopic study of the excised parathyroid glands showed diffuse hyperplasia of all cell types.

In March 1940, four and one-half months after the onset of the tetanic episode, the patient felt quite well. He continued to take calcium lactate and viosterol. The blood calcium was 10.2 mg and the phosphorus 3.6 mg per hundred cubic centimeters. If the taking of calcium lactate was discontinued for any length of time, he experienced tingling of the lips and hands. Roentgen studies of the long bones showed considerable recalcification. The weakness and lassitude of which he complained had improved markedly.

*Comment*—There are several interesting features about this case. The patient presented a fairly classic picture of primary hyperparathyroidism. He had no previous history of nephritis, although at the time of investigation in the hospital there was evidence of marked impairment of renal function. This may be explained, however, on the basis of previous renal calculus disease, since a stone had been removed from the urinary bladder five years previously. On operation, however, he had an adenoma of one parathyroid gland and hyperplasia of the remaining parathyroid glands, the former almost always seen in primary hyperparathyroidism. It is entirely possible that the hyperplasia of the parathyroid glands was secondary to the long-standing renal disease, while the latter was initially induced by the adenoma of the parathyroid gland (primary hyperparathyroidism) with formation of renal calculi.

After removal of the excessive parathyroid tissue, there occurred a considerable degree of improvement in the bony structure, although renal function continued to be seriously impaired. This is not entirely unexpected, since one would assume that the renal damage induced by the stones would be of an irreversible character. The tetany which developed was due to the excessive removal of parathyroid tissue.

**CASE 4**—R. T., a white woman 36 years of age, was admitted to the hospital for the first time in September 1936. She complained of attacks of pain in the right flank, radiating to the lower right abdominal quadrant and to the right thigh. The first such attack occurred four years prior to admission, and recurrent attacks appeared at approximately yearly intervals. She had no complaints referable to the bony structure at this time. Investigation in the hospital revealed the presence of bilateral renal calculi, and roentgen studies of the skeletal structure demonstrated the presence of some cystic changes in the left ilium. The skull and the long bones, however, were roentgenologically normal. The blood calcium varied from 11.8 to 13.0 mg and the phosphorus from 3.5 to 4.0 mg per hundred cubic centimeters. The total protein was 7.5 Gm per hundred cubic centimeters, and the blood phosphatase was 8 King-Armstrong units. Three day study of the calcium balance performed on two separate occasions showed the total urinary calcium excreted to be 1,070 and 1,332 mg, respectively, with a total calcium intake of 300 mg. Studies of renal function gave essentially negative results. The patient was discharged from the hospital for further observation in the outpatient department.

She was readmitted to the hospital in April 1937. She then complained of generalized aches and pains, particularly over the left scapula. The blood calcium was 11.6 mg and the phosphorus varied from 3.4 to 4.0 mg per hundred cubic

bones, in which the blood phosphatase is frequently elevated<sup>30</sup> This is by no means a hard and fast rule, however Rowntree<sup>31</sup> reported instances of multiple myeloma with increased values for blood phosphatase

CASE 7—K S, a white woman aged 39, was admitted to the hospital in April 1941, complaining of severe pains across the lower part of the back and shooting pains over the lateral and anterior aspects of the right thigh These pains had been present for approximately one month Roentgen studies revealed the presence of a compression fracture of the fourth lumbar vertebra with marked decalcification of this vertebra In addition, there was marked decalcification of the entire dorsal part of the spinal column and of the right innominate bone There was an ovoid area of decreased density of the right iliac crest, and there was a fracture of the sixth rib The blood calcium varied from 13.2 to 17.8 mg and the phosphorus from 3.7 to 5.3 mg per hundred cubic centimeters It is interesting that of eight determinations of blood calcium only one showed 13.2 mg per hundred cubic centimeters, the remaining seven determinations showed amounts that varied from 15.4 to 17.8 mg The blood phosphatase, which on admission was 9 King-Armstrong units, rapidly increased to 60 King-Armstrong units within six weeks The blood urea nitrogen varied from 18 to 53 mg per hundred cubic centimeters, while the carbon dioxide and total proteins were quite normal Tests of renal function gave essentially normal results, and there was no Bence Jones protein in the urine Biopsy of sternal marrow revealed the marrow to be normal A study of the calcium balance showed the total excretion of calcium over a three day period to be 1,500 mg, with an intake over this same period of 300 mg

It was evident that this patient had hyperparathyroidism, and since at this time no extraneous cause could be found, her neck was explored and four perfectly normal parathyroid glands were visualized Several weeks later she had a definitely palpable, although very small mass in the left breast, and at this time the left axillary lymph nodes were evident Biopsy of these nodes revealed carcinoma secondary to the carcinoma of the breast

*Comment*—This patient, therefore, had secondary hyperparathyroidism, secondary to carcinoma of the breast with extensive metastasis to the bones It should again be noted, as with the previous patient, that there were definite roentgenologic, chemical and metabolic changes of hyperparathyroidism in the absence of any gross changes in the parathyroid glands It is interesting to observe the elevation of the blood phosphatase in this instance in contrast with the previous case It is important to emphasize that the extensive bony changes present in these 2 cases were not due solely to the cancerous invasion of the bones but resulted in part from the hyperfunction of the parathyroid glands

#### *Cases of Hyperparathyroidism Secondary to Chronic Renal Disease*

CASE 8—L U, a white woman aged 18, was admitted to the hospital for the first time in 1941 She had apparently been well up to six weeks before admission At that time she noted swelling of the eyelids in the morning, some nocturia and no polyuria or hematuria In addition, she noticed the appearance of many hard lumps under the skin of the legs These lumps were painful on slight pressure For three weeks prior to admission she had noticed night sweats and a low grade fever The only significant point in her past history was an attack of scarlet fever at the age of 3 years

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31 Rowntree, L G Progress Relative to Diseases of the Ductless Glands, Pennsylvania M J 36 646, 1933

tory operation was therefore made, and an adenoma of the left lower parathyroid gland was excised. The remaining parathyroid glands appeared to be fairly normal in size.

Two days after operation the blood calcium fell to 8.4 mg and two days later to 7.3 mg per hundred cubic centimeters. The blood phosphorus remained at 3.3 mg per hundred cubic centimeters. Directly after the operation oliguria developed. The urea nitrogen rose to 69 mg per hundred cubic centimeters, and the carbon dioxide content fell to 29 volumes per cent. She was treated with solution of parathyroid, calcium, transfusions and alkalis. On the eighth post-operative day she contracted pneumonia, and on the tenth postoperative day she died.

*Comment*—This case is of interest because it once again demonstrates the chronicity of the disease. In all probability, the changes of the skull diagnosed roentgenologically as Paget's disease fifteen years before were the early changes of hyperparathyroidism. This patient presented evidence of marked renal failure. Because of this, the diagnosis of renal rickets was entertained. However, the considerable elevation of the blood calcium and the normal level of the blood phosphorus pointed sharply to primary hyperparathyroidism.

#### *Cases of Hyperparathyroidism Secondary to Multiple Myeloma and Carcinomatous Metastasis to the Bones*

CASE 6—C. B., a white woman of 68 years, was admitted to another hospital for the first time in December 1939. At that time she complained of pain and weakness of the left arm of several months' duration. Roentgenograms of the skeletal structure showed a cyst of the left humerus and considerable decalcification of the long bones. The blood calcium amounted to 14.2 mg and the phosphorus to 2.4 mg per hundred cubic centimeters. The blood and urine were otherwise found to be completely normal. She had a small, firm, rounded mass in the right lobe of the thyroid gland. It was felt that she had hyperparathyroidism and that an exploratory examination should be made. At operation all four parathyroid glands were visualized and found to be entirely normal in size. The right lobe of the thyroid gland was removed, and the small palpable mass was found to be an adenoma. The parathyroid glands removed with the thyroid tissue were studied histologically and found to be normal.

The patient was fairly well after operation for a period of several months, then she began to complain of pains in the back, the chest and the long bones. She now had marked anorexia, weakness, dyspnea and cough. She was admitted to the Mount Sinai Hospital in April 1941. Roentgen studies at this time showed innumerable areas of destruction in the cranial and facial bones and the long bones. There was extensive osteoporosis of the dorsal and lumbar vertebrae, with collapse of several dorsal vertebrae. The blood calcium was now 12.0 mg and the phosphorus 3.7 mg per hundred cubic centimeters. The phosphatase amounted to 6 King-Armstrong units. The urine showed Bence Jones protein and a sternal puncture showed innumerable plasma cells.

The diagnosis of multiple myeloma was now definite, and it was evident that the original early changes in the bones, the elevation of the blood calcium and the depression of the phosphorus were due to hyperparathyroidism secondary to this malignant disease. It is interesting to note that these changes were not associated with any evident changes either in the size or in the histologic appearance of the parathyroid glands. The blood phosphatase was normal, as it usually is in cases of multiple myeloma in contrast with cases of carcinomatous metastasis to the

stationary for nine years, then the pain in her back became more intense, and she noticed the onset of pains in other parts of her body, particularly in the knees. About five months prior to admission to the hospital she began to lose weight, suffered from anorexia and asthenia, and noticed increasing thirst and polyuria. Four months prior to her admission to the Mount Sinai Hospital she had been admitted to another hospital, where roentgen studies revealed a granular appearance of the skull, destructive changes in the acromion processes and a large cyst in the middle third of the left clavicle. The blood calcium amounted to 10.0 mg, urea nitrogen to 14.8 mg and creatinine to 10.8 mg per hundred cubic centimeters. No renal calculi were observed. The blood phosphatase was 23.4 Bodansky units. Biopsy of the cystic area in the left clavicle showed some scattered and some clumped multinuclear giant cells in a substratum of swollen connective tissue cells. In some places collagenization of what appeared to be miliary areas of hemorrhage were seen. At the periphery in some of the sections, small amounts of newly formed bone interspersed with connective tissue were observed. The pathologic diagnosis was "brown tumor" in a case of hyperparathyroidism.

Several weeks later the patient was admitted to the Mount Sinai Hospital wards. Roentgen examination of the skull showed a considerable increase in thickness of the cranium with obliteration of the diploe. There was coarse mottling throughout the calvarium. There was marked diffuse osteoporosis of the shoulder bones, and a large defect in the left clavicle was noted, as well as evidence of new bone formation around the periphery of this defect. There was diffuse osteoporosis of the long bones. There were mottling and thickening of the right pubis and ischium. The blood calcium varied from 11.1 to 12.4 mg and the phosphorus from 8.1 to 6.3 mg per hundred cubic centimeters. The urea nitrogen varied from 6.8 to 9.8 mg per hundred cubic centimeters. The creatinine was 10.0 mg per hundred cubic centimeters. The total protein, the total chloride and the cholesterol values were essentially normal. The phosphatase was 37 King-Armstrong units.

The patient was operated on, and four hyperplastic parathyroid glands were visualized, of which 2 were removed. Several weeks later the patient died in uremia. Permission for postmortem examination was not obtained.

*Comment*—Cases 8 and 9 are typical instances of chronic renal disease with secondary hyperparathyroidism. The signs and symptoms of progressive renal failure antedated the onset of the bony changes and the results of chemical studies of the blood were typical of severe renal insufficiency. In both instances all four parathyroid glands were markedly hyperplastic.

#### SUMMARY

Nine cases of hyperparathyroidism are reported. In 5 of these cases the condition was primary, due to adenoma of a parathyroid gland, and in 4 it was secondary, due to chronic renal disease, multiple myeloma and carcinomatous metastasis to the bones. The pathologic physiology, the clinical considerations and the treatment are discussed.



On examination her eyelids were found to be puffy. The ocular fundi were normal. The heart was not enlarged, and the blood pressure was 110 systolic and 50 diastolic. The radial arteries were thickened, and there was marked tortuosity of the left superficial temporal artery. There were many small, rounded, hard, tender subcutaneous plaques on both calves and around the ankles. On the skin of the axillas, the upper parts of the thighs and the buttocks there were innumerable pinhead-sized, firm, pinkish white papules. There was a considerable degree of anemia, the hemoglobin being 43 per cent and the red blood cell count 2,140,000. The blood urea nitrogen amounted to 120 mg per hundred cubic centimeters, the blood calcium to 10.4 mg and the phosphorus, determined on two occasions, to 8 and 10.5 mg. The total proteins amounted to 5.8 Gm per hundred cubic centimeters, of which the albumin component was 3.2 and the globulin 3.6 mg. The carbon dioxide content was 35 volumes per cent, the chlorides amounted to 560 mg, the cholesterol to 180 mg and the creatinine to 8.7 mg per hundred cubic centimeters. The blood phosphatase was 21 King-Armstrong units. The urine showed fixation of specific gravity at 1.012 and contained small amounts of albumin and some white blood cells, red blood cells and an occasional hyaline cast.

The roentgenograms were particularly interesting. The skull showed generalized mottling. The arms, legs and abdomen showed numerous calcific deposits distributed extensively throughout the soft tissues. There were extensive calcifications of the vessels of the extremities and of the pelvis as well as of the splenic artery. All of the bones of the extremities showed diffuse osteoporosis. The ribs revealed similar osteoporotic changes as well as numerous small areas of rarefaction. The lumbar vertebrae also revealed a generalized osteoporotic process. Biopsy of one of the subcutaneous nodules revealed it to be calcium.

It was felt that this patient had chronic diffuse glomerular nephritis with secondary hyperparathyroidism. Following several transfusions, her general condition was improved, and she was discharged from the hospital one month after admission.

The patient was readmitted in October 1941, approximately two months after discharge. Her clinical condition had become decidedly worse. Many of the calcific nodules had ulcerated through the skin, producing painful sloughing areas. The blood urea nitrogen was 78 mg, the calcium 10.0 mg and the phosphorus 9.7 mg per hundred cubic centimeters. The carbon dioxide content was 31 volumes per cent.

It was obvious on admission that the patient was near death, and on the third day in the hospital she died.

On postmortem examination the four parathyroid glands were found to be unusually large and hyperplastic, the largest gland measuring 30 by 20 by 18 mm. There was extensive deposition of calcium throughout the soft tissues of the body but particularly in the lungs and in the walls of the stomach. The kidneys showed the characteristic changes of chronic diffuse glomerular nephritis with marked contraction.

CASE 9—K. K., a white woman aged 49, was admitted to the hospital in December 1941 because of marked weakness, anorexia, loss of 19 pounds (8.6 Kg.), polydipsia and polyuria of five months' duration. Thirteen years before admission she began to have pains across the back at the level of the upper lumbar vertebrae. This pain persisted for two years before the condition was adequately investigated. It was then discovered that she had chronic diffuse glomerular nephritis and that the blood pressure was 186 systolic and 110 diastolic. Her symptoms were fairly

largely dependent on the collection of air in the mediastinum. The onset is abrupt without any preceding illness or injury. The first symptom is pain of a severe type either in the side of the chest or substeinally. When it begins in the side of the chest, it usually migrates to the substernal region or appears there after a pain-free interval. It may radiate to the neck or down the left arm and thus closely mimic the pain of coronary occlusion. The pain occasionally shows a slow steady increment in intensity, it is frequently markedly influenced by posture and often is accompanied by substernal tightness and a noise audible to the patient. A transient low grade fever has rarely been noted.

On examination of the patients, the pathognomonic sign described by Hamman is found. This is a peculiar crackling, crunching sound heard over the sternum and precordium which is synchronous with the heart beat. It may be heard with the patient in any position but frequently can be heard only with the patient in one position, such as lying on the left side. The area of impaired resonance to percussion normally present over the heart is in some instances replaced by hyperresonance. There may or may not be signs of pneumothorax, and a small amount of subcutaneous emphysema in the tissues of the neck or thorax is sometimes present. In a few instances rales have been described in isolated areas over the lung fields. The possibility of air traversing the aortic and esophageal openings in the diaphragm and appearing retroperitoneally has been mentioned but has not been described in any of the cases of spontaneous emphysema, although it is known to occur frequently in cases of emphysema due to thoracic trauma. Roentgenograms of the chest may or may not demonstrate the mediastinal air. A pneumothorax is occasionally shown. In 1 of the cases reported by Hamman there was minimal apical pulmonary tuberculosis, and in another case there was some increase in density at the base of the right lung which was interpreted as evidence of bronchiectasis. There have been no other roentgen signs of abnormality reported.

In all instances the process has been benign, complete recovery without sequelae occurring in several days. In a number of cases, however, there have been recurrences. Mediastinal compression sufficient to impede the circulation, which occurs not infrequently following trauma or in cases in which there is bronchial blockage due to foreign body, has not been present in these cases of spontaneous emphysema, although the possibility remains. No treatment has been required.

Considerable light has been thrown on the development of this condition through the experiments of Macklin,<sup>13</sup> largely with cats. By means of a ureteral catheter introduced into a bronchus, he has blown air into an isolated part of the lung, producing overdilatation of the alveoli in this area. The alveolar ectasia thus produced actually causes the bases of the alveoli to pull away from the underlying blood vessels and gives rise to a pressure gradient from alveolus to vascular sheath favorable to the passage of air into the vascular sheath. The air then passes along the sheaths of the blood vessels to the mediastinum. Air may also dissect along strips of connective tissue and give rise to blebs on the pleural surface. In man it is probable that rupture of these blebs gives rise to the pneumothorax which often accompanies interstitial emphysema of the lungs. Kirshner<sup>7</sup> expressed the opinion that this is probably the most frequent mode of development of benign spontaneous pneumothorax. In his experimental animals Macklin has found that air escapes

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13 Macklin, C. C. Pneumothorax with Massive Collapse from Experimental Local Overinflation of the Lung Substance, *Canad. M. A. J.* **36** 414-420 (April) 1937, Transport of Air Along Sheaths of Pulmonic Blood Vessels from Alveoli to Mediastinum. Clinical Implications, *Arch. Int. Med.* **64** 913-926 (Nov.) 1939.

# SPONTANEOUS INTERSTITIAL EMPHYSEMA OF THE LUNG

WITH MEDIASTINAL, RETROPERITONEAL AND SUBCUTANEOUS EMPHYSEMA

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The occurrence of interstitial emphysema of the lung with air within the mediastinum as a result of thoracic trauma has been recognized for a long time. It has, of course, been described by many observers following medical and surgical maneuvers involving the lungs and pleura and associated with foreign bodies in the bronchial tree. The occurrence of mediastinal air and subcutaneous air has also been described as a complication of many pulmonary diseases, including tuberculosis, influenza, bronchopneumonia of various types and asthma. It has been known to occur when the intrabronchial pressures were elevated by the use of positive pressure anesthesia and during the efforts of labor. Hamman,<sup>1</sup> however, was the first to report the condition in healthy persons without antecedent trauma or disease. It was in 1934 in a paper discussing the diagnosis of coronary occlusion, that Hamman presented 2 cases of spontaneous mediastinal emphysema which simulated coronary occlusion. He added 4 cases in a paper in 1937<sup>2</sup> and brought the total to 7 with a thorough discussion of the subject in 1939.<sup>3</sup> Since the recognition of the condition and the description of its clinical features by Hamman, other cases have been reported by Scott,<sup>4</sup> Morey and Sosman,<sup>5</sup> McGuire and Bean,<sup>6</sup> Kirshner,<sup>7</sup> Wolff,<sup>8</sup> Caldwell,<sup>9</sup> Matthews<sup>10</sup> and Pinckney.<sup>11</sup> Spontaneous mediastinal emphysema is apparently not uncommon in newborn infants, and the literature has recently been brought up to date by Gumbiner and Cutler.<sup>12</sup>

The clinical pictures encountered in all the cases of spontaneous interstitial emphysema of the lung thus far reported have been similar, and the condition is

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From the Medical Service "A" of the Pennsylvania Hospital and the University of Pennsylvania School of Medicine

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12 Gumbiner, B, and Cutler, M M. Spontaneous Pneumomediastinum in the Newborn, *J A M A* **117** 2050-2053 (Dec 13) 1941

## REPORT OF A CASE

N M, a white man aged 52, was admitted to the Pennsylvania Hospital on Sept 1, 1941. He had been first seen in the neurologic clinic in January 1930, complaining of loss of strength and feeling in his left hand. He stated that he had had a penile lesion at the age of 22 and that he had received a few "shots for his blood" in 1926. Fixed pupils, absence of knee jerks and a definite ulnar palsy were noted, and a diagnosis of syphilis was made. The Wassermann reaction of the blood and of the spinal fluid was 4 plus, and the colloidal gold curve was of a dementia paralytica type. He received intermittent antisyphilitic therapy from that time until he was admitted to the hospital, on Sept 1, 1941, specifically for fever therapy. The serologic reactions of his blood and spinal fluid had remained consistently positive. His only complaint on admission was a slight headache.

On examination he appeared well developed but somewhat poorly nourished. He was oriented, cooperative and presented none of the mental changes associated with dementia paralytica.

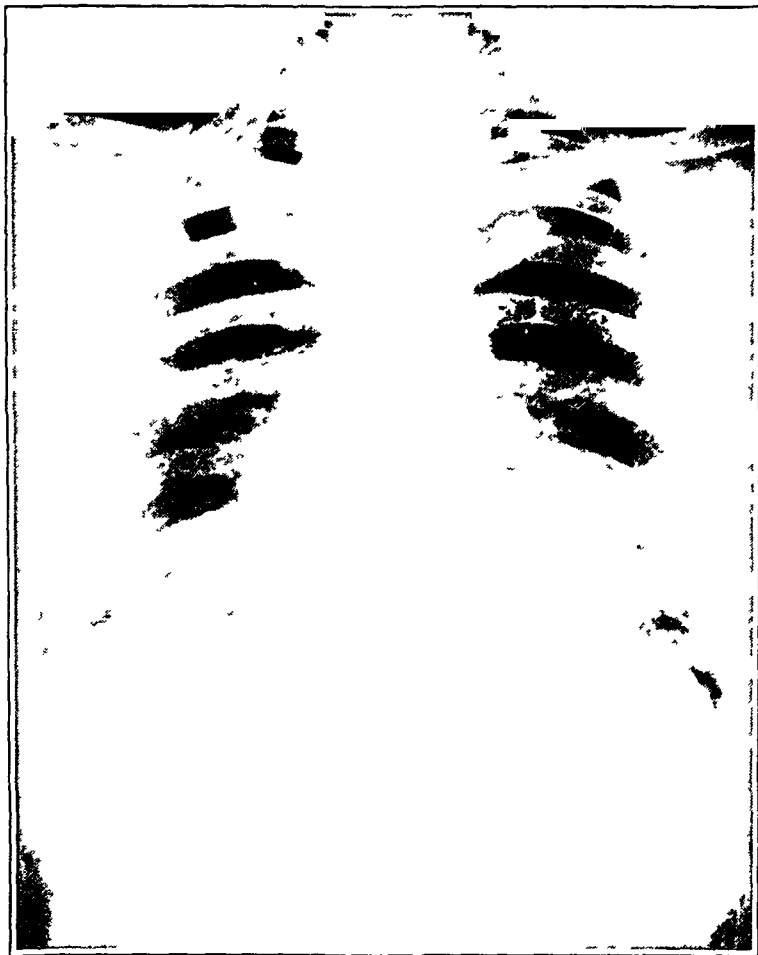


Fig 2—A roentgenogram taken during expiration on September 22 to rule out the existence of pneumothorax. The density at the base of the left lung can be seen to better advantage than in figure 1.

The temperature, pulse and respirations were normal, and the blood pressure was 110 systolic and 70 diastolic. The pupils were small and slightly irregular and failed to react to light. There were dental caries, and moderate pyorrhea, and the pharynx was slightly reddened. No abnormalities were noted in examination of the heart, lungs or abdomen. The knee jerks were absent, sensation was grossly normal. There were no abnormalities of sphincteric control. The urine was normal. The blood count showed 3,400,000 red blood cells and 7,500 white blood cells, with a normal differential count, there was 12 Gm of hemoglobin per hundred cubic centimeters. The phenolsulfonphthalein excretion and the electrocardiogram were normal.

On September 10 fever treatments were started, each one consisting of approximately five hours' elevation of temperature to 105.6 F in the Liebel-Flarsheim air-conditioned hypertherm. On the evening of September 19, after the fifth period of fever therapy, the patient noted a chilly sensation of short duration, and his temperature rose to 100.6 F. At the same

into the pleural space through rents in the mediastinal pleura, and this may also be the course in man. Air does not enter the mediastinal structures from a pneumothorax space, however, even in the face of high intrapleural pressures.

In experimental animals it is the insufflation of air which distends the alveoli and gives rise to the leakage of air. Macklin points out that atelectasis of an area of lung may likewise lead to overdistention of surrounding alveoli, with the same resultant pressure gradient from alveolus to vascular sheath and consequent perivascular emphysema. In support of this Fisher and Macklin<sup>14</sup> reported a careful pathologic study of a child with foreign body atelectasis of the right lung and consequent distention of the left lung. They were able to demonstrate the alveolar ectasia in the left lung with the air in the vascular sheaths leading to mediastinal emphysema. Because it seems unlikely that perfectly normal alveoli in their normal

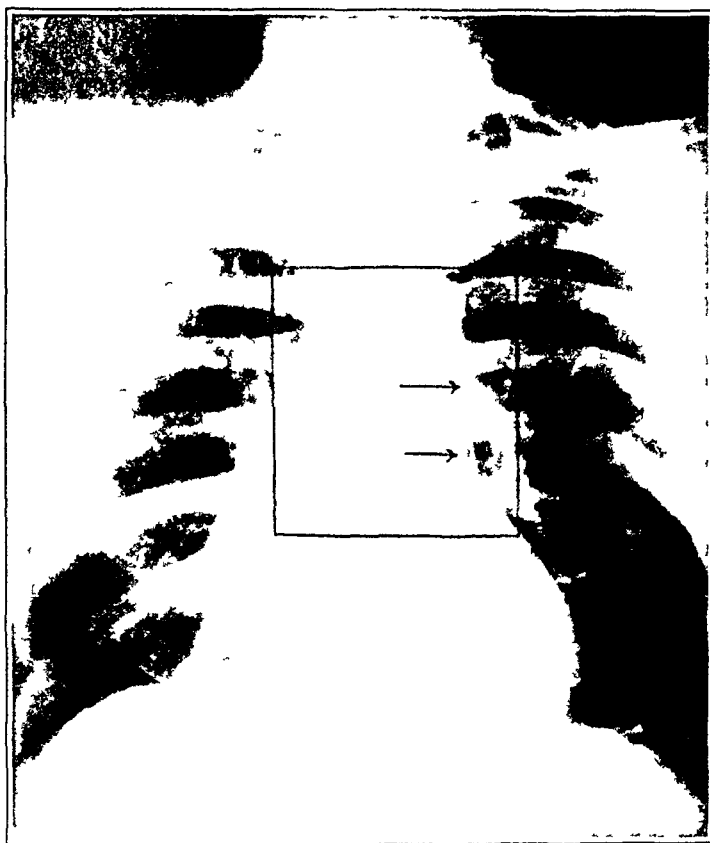


Fig 1—Posteroanterior roentgenogram of the chest taken Sept 22, 1941. The arrows within the inset show the air distending the mediastinal pleura. At the base of the left lung the small dense area and the emphysema with paucity of lung markings above it can be seen. There is a calcified primary lesion of tuberculosis in this area.

anatomic relationships would allow the leakage of air. Macklin<sup>15</sup> has emphasized the need for a careful roentgen search for small atelectatic areas in persons with so-called spontaneous interstitial emphysema of the lung. The following case of interstitial emphysema of the lung has several interesting features.

14 Fisher, J. H., and Macklin, C. C. Pulmonic Interstitial and Mediastinal Emphysema. Report of a Fatal Case in Which the Emphysema Occurred in a Child as a Result of the Aspiration of Peanut Fragments, *Am J Dis Child* 60:102-115 (July) 1940.

15 Macklin, C. C. Spontaneous Mediastinal Emphysema. A Review and Comment, *M Rec* 150:5-7 (July 5) 1939.

time he complained of scrotal swelling. This was not examined carefully and was interpreted first as angioneurotic edema. The following morning the temperature was normal, but widespread subcutaneous emphysema was present.

The patient first came under my observation on September 21, at which time his temperature, pulse, respirations and blood pressure were normal. He stated that he had had no pain at any time. On examination there was subcutaneous emphysema on both sides of the neck, on the left side of the thorax anteriorly, on the entire abdomen and in the region of the sacrum. The scrotum and penis were distended with air, and subcutaneous air extended down the left leg to the knee. Air could be felt in the tissues around the rectum by digital examination. The area of normal cardiac dulness was intact, but on auscultation over the sternum the crackling, crunching noises described by Hamman were clearly heard. They were synchronous with the heartbeat and could be heard throughout the cardiac cycle. They were independent of respiration and could be heard best with the patient in the recumbent position, although they were audible with him in any position. There was definite hyperresonance over the lower



Fig 5—A roentgenogram of the abdomen taken September 29, showing the small amount of residual air in the retroperitoneal spaces

part of the left side of the chest posteriorly, and over this same area there were inspiratory crackling sounds which bore a striking resemblance to those sounds just described as occurring over the precordium. There was no subcutaneous emphysema over this area to confuse the findings. A roentgenogram taken the following morning (fig 1) showed evidence of mediastinal air. There was a small density at the base of the left lung which was interpreted as an area of atelectasis. Just above this there was an area of greater penetration which suggested an area of lung containing a larger than normal amount of air. A small amount of subcutaneous emphysema could be seen in the neck. A roentgenogram was obtained during expiration (fig 2) to make certain that a small pneumothorax was not overlooked, and none could be demonstrated. A roentgenogram of the abdomen showed a striking amount of retroperitoneal emphysema (fig 3).

The signs rapidly disappeared, and by September 29, eight days later, nothing abnormal could be detected on examination of the patient. Another roentgenogram of the chest on that date (fig 4) showed a return to normal with complete disappearance of the small area

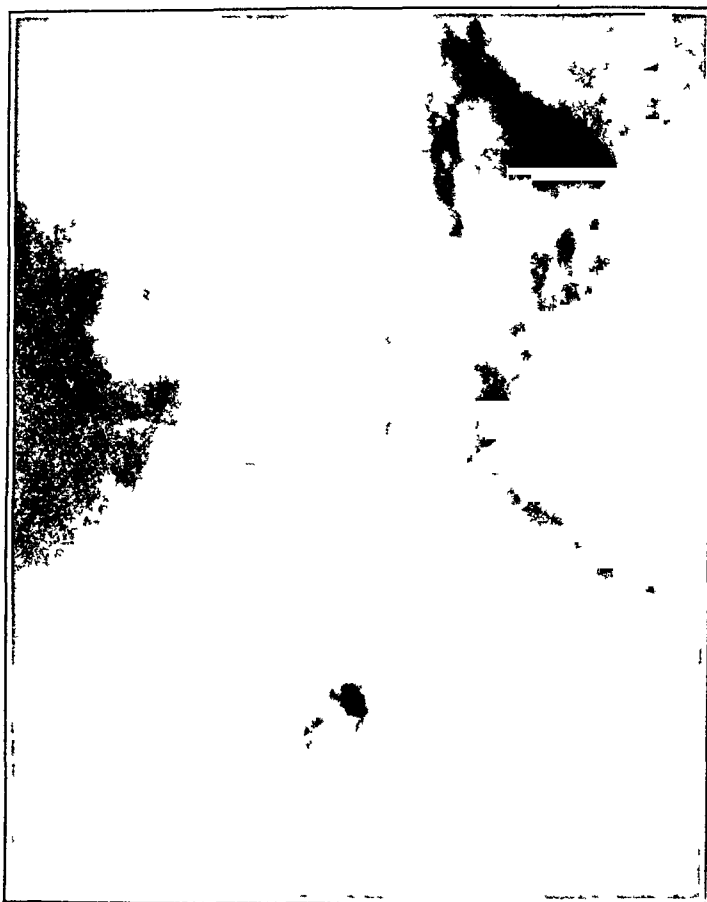


Fig 3—A roentgenogram of the abdomen taken September 23, showing the marked retroperitoneal emphysema outlining the kidneys



Fig 4—A posteroanterior roentgenogram of the chest taken September 29, showing the return to normal. The small density at the base of the left lung is now gone

"pericardial knock" which has been described thoroughly by Lister<sup>17</sup> and that one hears at times during the course of therapeutic pneumothorax. Four cases have been observed during the last few years in which pericardial knock appeared for a time shortly after induction of therapeutic pneumothorax on the left side. In these cases the sound was a very loud, single, slapping sound, which was frequently palpable. Its intensity was greatest near the apex of the heart, and it was systolic. The sound was usually heard only with the patient lying on the left side and during one phase of the respiratory cycle. While the mechanism of production of this sound is not completely understood, it is felt that it was due to the pneumothorax and not to air within the mediastinum. A great deal of care must be exercised in differentiating pericardial knock from those sounds occurring as a result of air within the mediastinum. It is certainly true, however, that interstitial emphysema of the lung may lead to both mediastinal air and spontaneous pneumothorax in some cases.

No connection could be demonstrated between either the syphilis or the fever therapy used as treatment and the development of the emphysema in this case.

#### SUMMARY AND CONCLUSIONS

The literature regarding the clinical picture and pathogenesis of spontaneous interstitial emphysema of the lung has been reviewed.

Spontaneous interstitial emphysema of the lung with extension of air into the mediastinum commonly gives rise to subcutaneous emphysema in the neck. The air may also escape the mediastinum to the retroperitoneal spaces and produce subcutaneous emphysema in the lower part of the body. This may explain the presence of subcutaneous air in many otherwise puzzling situations.

A case of spontaneous interstitial emphysema of the lung with extension of air into the retroperitoneal and subcutaneous tissues is reported. The absence of pain in this case may have been due to the ease of escape of the air from the mediastinum, which prevented the development of high mediastinal pressures.

A small area of transient atelectasis was apparently responsible for the development of the interstitial emphysema of the lung in this instance. It was possible to locate clinically the site of escape of air from the alveoli into the perivascular and interstitial tissues of the lung.

It is felt that the auscultatory signs produced by air within the mediastinum differ in type and mode of production from the so-called "pericardial knock" sounds occasionally occurring in left-sided pneumothorax whether spontaneous or induced.

University Hospital

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<sup>17</sup> Lister, W. A. Pericardial Knock Associated with Spontaneous Pneumothorax, *Lancet* 2: 1225 (Dec. 26) 1928.



of density at the base of the left lung and the area of emphysema above it. A roentgenogram of the abdomen (fig 5) showed almost complete absorption of the retroperitoneal air. At this time the patient's vital capacity was 3,500 cc. Blowing against resistance failed to reproduce the abnormality. The fever treatments were reinstituted on October 1 and were continued to a total of twelve without any untoward reactions.

#### COMMENT

There are several points of interest illustrated by this case. In most of the cases thus far reported, pain has been a prominent feature and has focused the attention of the clinician on the mediastinum with the subsequent recognition of the pathologic process. The fact that large amounts of air can escape from the lungs and appear in the retroperitoneal and subcutaneous tissues without causing any pain may help to explain the origin of aberrant air in many puzzling situations. Two cases have recently been observed, one of terminal uremia and another of a pelvic abscess, in which there was unexplained subcutaneous emphysema of the abdominal wall. In neither case was there definite clinical evidence of air in the mediastinum, although it is highly probable that the subcutaneous air came from this source. The typical signs of mediastinal emphysema might conceivably be lacking if the air escaped readily from the posterior mediastinum and did not accumulate anteriorly.

The increase in mediastinal pressure is probably the factor which determines the production and severity of pain. It is therefore safe to assume that the case with which air escapes the mediastinum is an important factor also. In this case there was apparently a safety valve from the mediastinum by way of the aortic and esophageal openings in the diaphragm. In this connection, it is interesting to recall the experiences of Torrey and Grosh<sup>16</sup> in an Army camp during the influenza epidemic of 1918. They found that in the cases in their locality there was considerable pulmonary and mediastinal emphysema among the afflicted persons. The patients had enlarged, hyperresonant chests with engorgement of the veins in the neck and suffered considerable pain. Those patients in whose necks large amounts of subcutaneous emphysema appeared showed striking and immediate improvement due to the release of mediastinal pressure.

It is also of interest that the site of alveolar leakage could be lateralized clinically. The hyperresonance and the peculiar crackling, crunching rales found at the base of the left lung and resembling those sounds heard over the mediastinum, were considered sufficient to determine this. The suggestive changes in the roentgenograms were considered to be confirmatory.

The finding of a small area of atelectasis in the roentgenogram is intriguing in the light of Macklin's suggestion that atelectasis leads to distention of surrounding alveoli with subsequent leaking of air into the vascular sheaths. There is an alternate hypothesis to explain this density, that is, that the surrounding emphysema could have compressed this small area represented by increased density in the roentgenogram. It seems most likely, however, that this density does represent an area of atelectasis.

The sounds heard over the mediastinum in this case were due entirely to air within the mediastinum. They were audible during systole and diastole and throughout the respiratory cycle. They were somewhat louder when the breath was held in the expiratory phase. These sounds differed entirely from the so-called

16 Torrey, R. C., and Grosh, L. C. Acute Pulmonary Emphysema Observed During the Epidemic of Influenzal Pneumonia at Camp Hancock, Georgia, *Am J M Sc* **157** 170 (Feb) 1919.

The present communication concerns a family which has been affected with the Spuiway syndrome through at least four generations, in which there has been no consanguinity. The family is of Scotch-English lineage. A genealogic tree has been outlined (fig 1) accounting for 52 members. The data used to construct the genealogic tree were supplied by patients 7, 10 and 11, by patient 4, an uncle of patient 7, and by a cousin of patient 7, a physician (an unaffected member of the family). G M, patient 7, knew all members of the family except patient 1, information about the latter was supplied by patient 4. The family is well aware of their abnormality. Twelve members of the family possess one or all of the features of the disease. One has only blue scleras. Seven have both blue scleras and brittle bones. Four have all three defects. Eight of the affected ones are males, 4 are females. Of 14 males exposed to the risk of inheriting the syndrome, 7 did inherit it. Of 10 females similarly exposed, 4 showed the syndrome. Thus,

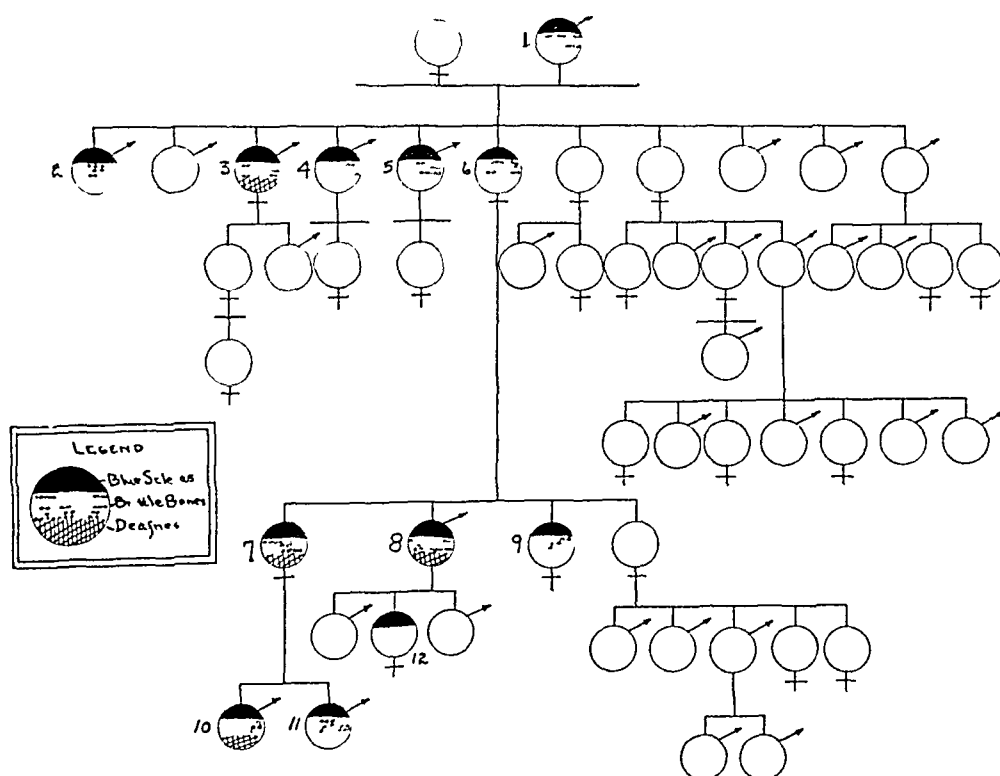


Fig 1—Genealogic tree of family

of 24 children of seven matings heterozygous in respect to the phenotype under discussion, 11 inherited the anomaly. Transmission by a male parent occurred in 2 instances and by a female in 2 instances. Transmission took place directly between succeeding generations. The inherited factor thus appears to be a mendelian dominant and not sex linked.

#### CASE ABSTRACTS

The numbers used to designate patients in the following abstracts correspond to those on the genealogic tree.

1 D C, an only son, had blue scleras and easily fractured bones. No information as to the number of fractures is available. He was slight, frail and of small stature. He died as a result of an abscess of the brain complicating acute mastoiditis. He was not known to be deaf. It is said that many of his relatives had blue scleras. His wife did not have the affliction. There is no information as to her family.

2 C C, a son of D C, had blue scleras and brittle bones. He died of pulmonary tuberculosis at the age of 27. No deafness had developed.

# BLUE SCLERAS, BRITTLE BONES AND DEAFNESS

A REPORT OF AN AFFLICTED FAMILY

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For centuries physicians have witnessed the tragic instance of a child born with multiple fractures of the bones. Lobstein<sup>1</sup> in 1833 designated this condition as osteopsathyosis—a descriptive term derived from Greek meaning friable bones. In 1849, Vrolik reported a similar condition, which he named osteogenesis imperfecta, implying defective formation of bone as the cause. Spurway,<sup>2</sup> in 1896 reported the first instance in which the condition of fragile bones (*fragilitas ossium*) was associated with blue scleras. Bronson,<sup>3</sup> in 1917, and van der Hoeve and de Kleyn,<sup>4</sup> in 1918, added to the syndrome the third feature—deafness. Key,<sup>5</sup> in 1926, referred to the syndrome as “hereditary hypoplasia of the mesenchyme” and called attention to the hypotonicity of the ligaments with hypermobile joints. In 1928 Bell<sup>6</sup> collected 75 pedigrees including 489 cases of this abnormality. The condition is not so rare as is generally thought.

Recent literature<sup>7</sup> has shown renewed interest in the syndrome and indicates that there are essentially two schools of thought regarding the cause of the brittle bones, the one asserting that the disease is a developmental defect, the other, that it is a metabolic dysfunction. The first theory resulted from Key's study, the second followed the suggestion that the parathyroid glands<sup>8</sup> were responsible. Critics<sup>9</sup> of the latter theory have published data which suggest that the parathyroid glands are not implicated and that any association of dysfunction of these glands with the syndrome is fortuitous.

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4 van der Hoeve, J., and de Kleyn, A. Blaue Sclera, Knochenbruechigkeit und Schwerhorigkeit, *Arch. f. Ophth.* 95: 81 (Jan.) 1918.

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7 (a) Hills, R. G., and McLanahan, S. Brittle Bones and Blue Sclerae in Five Generations, *Arch. Int. Med.* 59: 41 (Jan.) 1937. (b) Dessoff, J. Blue Sclerotics, Fragile Bones and Deafness, *Arch. Ophth.* 12: 60 (July) 1934.

8 Takahashi, T. Beitrag zur Kenntnis der blauen Sclera, *Arch. f. Ophth.* 115: 206, 1925. Dessoff<sup>7b</sup>.

9 Rados, A., and Rosenberg, L. C. Relation Between Blue Scleras and Hyperparathyroidism, *Arch. Ophth.* 16: 8 (July) 1936.



Fig 2—Profile view of patient 10

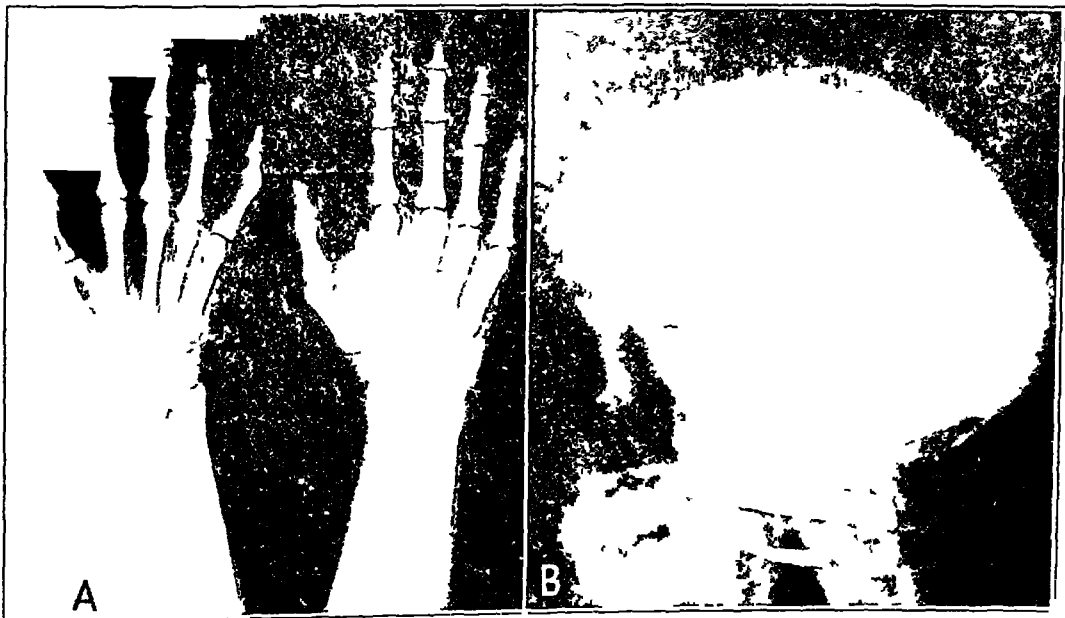


Fig 3—*A*, roentgenogram of a hand and forearm of patient 10 with that of a normal person for comparison, showing mild osteoporosis and old fracture of the little finger *B*, roentgenogram of the skull of patient 10, lateral view, showing the increase in anteroposterior diameter and the prominent occiput

3 E C, a son of D C, is alive and well at the age of 65. He has blue scleras and brittle bones and is deaf. No information is available as to the exact number of fractures he has had, but there have been many.

4 G C, a son of D C, is alive and well at the age of 70. He has blue scleras and has had an unknown number of fractures but is not deaf.

5 W C, a son of D C, had blue scleras and brittle bones. He was apparently not deaf.

6 C C S, a daughter of D C, had both blue scleras and brittle bones. There was at least one recognized dislocation, and she was small of stature. She died at the age of 74 years. There is good evidence that she was not deaf.

7 G M, aged 50, a granddaughter of D C, was interviewed and examined. She stated that she had sustained several fractures and numerous sprains in the course of her life, often caused by only slight trauma. She complained of having weak arches of the feet. During the past several years she had noticed progressive deafness. She related that she had a dietary idiosyncrasy, which is a family characteristic, i. e., she abstained from drinking milk. Physical examination revealed a healthy-appearing woman of 50 years. Her scleras were dark slate blue, and her hearing (watch test) was definitely impaired. She was small in stature (height 5 feet [152.5 cm]) but well proportioned. All other physical findings were normal. Roentgenograms showed the various bones to be slender and definitely osteoporotic. Laboratory studies showed blood calcium 10.7 mg and blood inorganic phosphorus 3.7 mg per hundred cubic centimeters, blood phosphatase 47 Bodansky units (corrected), total proteins 7.2 mg per hundred cubic centimeters. Gastric analysis revealed normal acidity.

8 W S, aged 42, alive and well, is a brother of G M. He has blue scleras, is deaf and has suffered more than twenty fractures in the course of his life, most of these occurring in youth. He is described as being small of stature. Physical examination was not performed.

9 G S died in childhood. She had blue scleras and brittle bones but was not deaf.

Patients 10 and 11 were examined at the Mount Morris Tuberculosis Hospital, Mount Morris, N. Y. Dr. N. Stanley Lincoln, superintendent, gave us permission to publish the data concerning them.

10 G O M, a great grandson of D C, was 25 years old at the time of examination. Since the age of 3 years he had had multiple fractures following slight trauma. On one occasion, while "climbing" on a horizontal bar, he broke an elbow. On another occasion he struck an arm against a wall and sustained a broken forearm. Most of his fractures occurred between the ages of 3 and 16 years, although recently he suffered a fracture of the left zygoma. There has been little or no displacement of the fracture segments. The location of the fractures were as follows: the left clavicle, a rib, the left zygoma, a phalanx (toe), the forearms, the elbows, the wrists, phalanges (fingers). Deafness and tinnitus were noticed for the first time at the age of 22 years and since have become progressively worse. He is able to hear low tones better than high tones. Since the onset of the deafness he has worn a hearing device. He, too, never drank milk and complains of having weak arches. He stated that his teeth erupted prematurely and that they decayed easily. Several extractions were necessary, and it was noted that the gums bled rather freely. The patient is frail and small of stature, and appears ten years older than his stated age. His height is 5 feet 4½ inches (164 cm), his weight, 103 pounds (46.5 Kg). His skull is large, but the facial features are small. His head has a relatively long anteroposterior diameter. The frontal and temporal areas are also rather prominent (fig. 2). Vision and the eyegrounds are normal. The scleras are china blue, the blue being most marked near the cornea and fading off slightly at the periphery. There is no evidence of keratoglobus. Otologic examination revealed a normal appearance of the drumheads. Tubal inflations gave no relief from the deafness. The Rinne test was negative, the Weber test showed hearing to be the same in both ears, and bone conduction is normal. The upper extremities show residual deformities from previous fractures. The humeri appear shortened. There is definite thickening about the elbow joints, with marked irregularity in the contour of both elbows. There is atrophy of the triceps muscles, particularly on the left. The forearms are small and free from deformity except in the immediate vicinity of the elbows. The finger tips are spatulous. The heart and the lungs were found normal. The blood pressure was 120 systolic and 80 diastolic. The remainder of the physical examination gave essentially negative results. Special studies included roentgen examination of all the bones, chemical analysis of the blood, gastric analysis and determination of the amount of calcium excreted in the urine and of the  $pH$  of the stools. Roentgenograms of the patient's bones, compared with those of an apparently normal person, taken simultaneously, showed generalized increased radiability, which is interpreted as osteoporosis (fig. 3A). The skull

four fractures and repeated dislocations on slight trauma. He, too, has always refrained from drinking milk. Physical examination revealed a healthy young man with china blue scleras. He demonstrated "double jointedness" with marked hypotonicity of the ligaments. There was marked irregularity in the contour of each elbow, with thickening about the elbow joint, and a small portion of the left olecranon process was felt posterior to the lower end of the humerus and was freely movable. These were residues of fractures. There was no deafness. Roentgenograms showed that all the bones were slender and small in size, with varying degrees of osteoporosis. The olecranon process of the left ulna showed an old fracture with displacement upward and posteriorly to the articular surface of the humerus (fig. 4).

12 C S, aged 6 years, a daughter of W S, is alive and well. She has blue scleras but has not as yet shown any tendency toward fracture or dislocation of bones or toward sprains. Her hearing is unimpaired.



Fig 4—Roentgenogram of the elbow regions of patient 11, showing osteoporosis and deformity following fractures

#### COMMENT

There is sufficient evidence that the syndrome under discussion is inherited. The present series conforms to the previously established dictum that unless blue scleras are present, the other features of the syndrome do not appear. Thus, the most constant feature of the syndrome is the scleral imperfection. The exact nature of this inherited anomaly is unknown. Whether a separate gene is concerned in the genesis of each feature of the syndrome is also unknown. Patients 7, 10 and 11 of the series have scleras varying from light blue to dark slate blue. The color was reputed to have varied similarly in those of their ancestors who had blue scleras.

It has been demonstrated that the majority of persons afflicted with the blue sclera syndrome are physically frail and small of stature. A characteristically shaped head has been frequently noted. In the affected persons whom Bronson<sup>2</sup> described there was unusual prominence of the frontal and occipital bones, one

showed an increase in both the anteroposterior and the bitemporal diameter. The occiput was unusually prominent (fig 3B). Chemical analysis of the blood gave results as follows: blood sugar 100 mg, nonprotein nitrogen 27 mg, urea nitrogen 11 mg, uric acid 3 mg, blood chlorides (as sodium chloride) 471 mg, calcium 9.9 mg, inorganic phosphorus 3.4 mg and total proteins 8.1 mg per hundred cubic centimeters, phosphatase activity 27 units (Bodansky). Gastric analysis following an alcohol test meal revealed the absence of free hydrochloric acid, a total acidity of 9 and a  $p_H$  of 6.3. A second test was then performed. The first sample was withdrawn after a test meal and the other samples at one-half hour intervals after injection of 0.5 cc of histamine base (histamine acid phosphate). The usual effects of histamine, such as flushing of the face, throbbing sensations in the head, tachycardia and fall in blood pressure, were observed, but no free hydrochloric acid was secreted. The results are given in table 1.

The excretion of calcium in the urine was determined in two test periods while the patient was on a diet, the calculated (but not analyzed) composition of which was planned to provide a neutral ash, low calcium content<sup>10</sup>. The pertinent data are charted in tables 2 and 3. These

TABLE 1—*Gastric Analysis After Stimulation with Histamine*

Sample	Total Acid	Free HCl	$p_H$	Blood	Microscopic Observations	Pepsin	Rennin	Mucus
1	5°	0	7.5	—	0	Slight	Slight	1—
2	15°	0	7.0	++	0	Slight	Slight	4+
3	25°	0		—	0	Normal	Normal	4+
4	35°	0		±	0	Normal	Normal	4—

TABLE 2—*Urine Calcium Excretion First Test*

Day	Intake of Calcium, Gm (Amount Calculated)	Excretion of Calcium, Gm (Urine Analyzed)
1	0.21	
2	0.22	0.260
3	0.22	0.165
4	0.20	0.145

TABLE 3—*Urine Calcium Excretion Second Test*

Day	Intake of Calcium, Gm (Amount Calculated)	Excretion of Calcium, Gm (Urine Analyzed)
1	0.13	
2	0.22	
3	0.17	
4	0.14	0.220
5	0.18	0.135

data showed an excretion of calcium in the urine somewhat in excess of the normal expectancy established by Aub and Farquharson<sup>10</sup> under similar controlled dietary restrictions. However, the excess is small and the period of observation short. It therefore appears highly improbable that there was any hyperparathyroidism, at least at this period of the patient's life.

The  $p_H$  of the stools, determined by a glass electrode on various occasions, varied between 7.2 and 5.6. The urine had a specific gravity of 1.015 and contained no albumin, sugar or abnormal cellular constituents. The Mosenthal test of renal function showed normal concentrating and diluting power, the specific gravity ranging from 1.005 to 1.021. The blood showed a hemoglobin content of 15.2 Gm, the red cell count was 5,110,000, the white cell count was 10,500, with myelocytes 0 per cent, juvenile forms 0 per cent, stab forms 2 per cent, segmented forms 35 per cent, eosinophils 3 per cent, mononuclears 10 per cent and lymphocytes 50 per cent. The bleeding time was six minutes, the clotting time was seven and one-half minutes (capillary pipet). The basal metabolic rate was  $-8$ . Complement fixation tests for syphilis were negative.

11 W. M., aged 19 years, a son of G. M., was examined by us. He related a history (confirmed by his mother) of having been born with a dislocated hip and of having sustained

10 Aub, J. C., and Farquharson, R. F. Studies of Calcium and Phosphorus Metabolism in Various Metabolic and Bone Diseases, *J. Clin. Investigation* 11: 235 (Jan.) 1932.

attempt to implicate the parathyroid glands pathogenetically. There is fairly good histologic evidence<sup>5</sup> that patients with this syndrome have a defective osteoid matrix, particularly in intramembranous ossification. This is most likely genotypic in origin. Whether there is a second defect of calcium deposition metabolic in nature but likewise genotypic in origin is impossible to say. Further speculation with the limited data available is certainly fruitless.

#### SUMMARY

This study presents a previously unrecorded family of 52 members, 12 of whom have been affected with the blue sclera syndrome. Seven of the 12 members have both blue scleras and brittle bones. Four have these defects and deafness, and 1 has so far only blue scleras. Eight of the affected members are males, 4 are females. The condition is transmitted from generation to generation and occurs equally in both sexes. The physical attributes of small stature, hypermobility of the joints, relaxation of the ligaments and, often, abnormal shape of the head are found characteristically in involved members. Three members of the group have been studied in detail. Roentgenograms of the skeleton revealed slender bones, generalized osteoporosis and deformities resulting from multiple fractures. The present series conforms to the classic description of the syndrome as outlined by John Spurway (1896) and elaborated further by Bronson (1917), van der Hoeve and de Kleyne (1918) and Key (1926).

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group having the type of skull which characterizes patients with osteogenesis imperfecta. Patient 10 of the present series has prominent frontal and occipital areas of the skull. The head is disproportionately large. Patients 7 and 11 have heads of normal size and shape. However, these 3 members are small boned and except for patient 11 are small of stature. They have noted that those of their collaterals who have white scleras tend to be either of average height or taller than normal.

Deafness has developed in 4 of the affected members. Because several members of the family are yet quite young, deafness may still occur in them. The syndrome in patient 10 conformed almost entirely with Bezold's syndrome, which establishes a diagnosis of otosclerosis with ankylosis of the stapediovestibular joint. However, as previously noted, he was able to hear low notes by bone conduction, whereas in otosclerosis the reverse is true.

Seven of the members with blue scleras have bones that show a tendency to fracture easily. Several members complain more of sprains and dislocated bones than of fractures. A characteristic of patients 7, 10 and 11 is that they have weak arches. Patients 10 and 11 show a predilection for fractures about the elbow joints, where their principal deformities are seen.

The clinical and roentgenographic evidences of poor mineralization of the bones suggest excessive excretion of calcium, deficient absorption of calcific salts or idiosyncrasy of alimentation. Although 2 patients of the family under discussion habitually had dietary restrictions that might have been significant, it is quite unlikely that these dietary abnormalities occurred selectively in members of a family through four generations. One patient has gastric achlorhydria even after stimulation with histamine and this as is well known<sup>11</sup> might lead to difficulties in the absorption of calcium from the intestines. However, we do not know whether this is merely an isolated individual aberration or a phenomenon occurring generally in persons with this syndrome. Several investigators<sup>12</sup> have reported cases in which the calcium balance was negative whereas others<sup>13</sup> found the calcium balance normal. Rados and Rosenberg<sup>9</sup> found normal excretion of calcium and phosphorus in the urine of their 2 patients. Since it seems well established that there is osteoporosis in this disease the fact that there is lacking unequivocal chemical evidence of a negative chemical balance appears to us to be of lesser significance. Certainly a degree of calcium loss that could be determined with ease in necessarily short term metabolic studies would be incompatible with the longevity of life demonstrated in the afflicted members of this family. It is also conceivable that negative phases of calcium balance might occur only during certain restricted times in their lives, and it would be a matter of chance that these should be discovered. Certainly the tendency to fracture seems to be a recurring, cyclic affair and diminishes with increase in age. This might conceivably be associated with endogenous changes, or it might be due to the varying exposure to risk of fractures at different times of life and the growing apprehension and personal solicitude that would come with maturity. Neither studies of phosphatase nor determinations of urinary calcium as done by others<sup>9</sup> and in the case of patient 10 warrant any

11 Zucker, T. F., and Matzner, M. J. On the Pharmacological Action of the Anti-rachitic Active Principle of Cod Liver Oil, *Proc Soc Exptl Biol & Med* **21** 186, 1923-1924.

12 Hunter, D. A Case of Osteogenesis Imperfecta, *Lancet* **1** 9 (Jan 1) 1927. Tauber, M. Beitrag zum Calciumstoffwechsel bei Osteogenesis imperfecta, *Monatschr f Kinderh* **36** 12, 1927. Aub and Farquharson<sup>10</sup>.

13 Sindler, A. Der Stoffwechsel bei Osteogenesis imperfecta, *Ztschr f Kinderh* **42** 85, 1926. Stevenson, G. H., and Cuthbertson, D. P. Blue Sclerotics and Associated Defects. Study of Four Families with Notes on Their Mineral Metabolism, *Lancet* **2** 782 (Oct 10) 1931.

Roentgenogram 4 was taken of the same cadaver placed in a left anterior oblique position

Roentgenogram 5 was taken of a cadaver in the dorsoventral position after injection of 35 cc of a 50 per cent sodium iodide solution and resection of the second and seventh costal cartilages

Other roentgenograms were taken, but they either were not clear enough for a correct interpretation or did not afford us more information than was furnished by the five sent with this paper

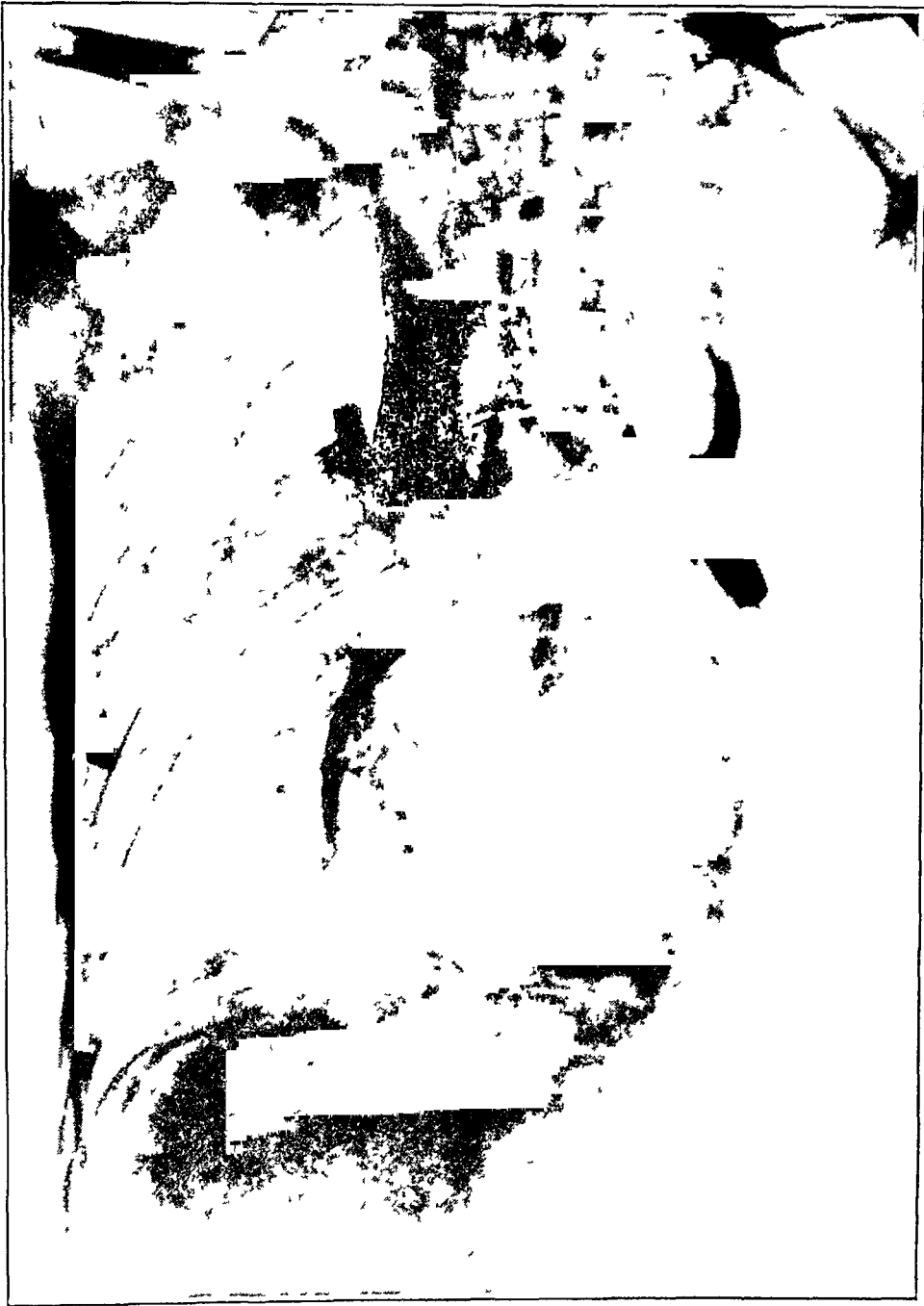


Fig 1—Vessels and right chambers of the heart of a cadaver in the dorsoventral position. The roentgenogram was taken after injection of 70 cc of sodium iodide solution into the superior vena cava and resection of the second and third costal cartilages

#### STUDY OF THE ROENTGENOGRAMS

1 *Vessels and Right Chambers of the Heart in the Dorsoventral Position (fig 1)*—The right innominate vein (more than 50 mm long and 10 mm wide) is nearly vertical, forming an angle of 10 degrees with the vertical axis. The left innominate vein is only partially opaque. Its direction is nearer to the horizontal with which it forms an angle of 40 degrees.

# NORMAL CARDIOVASCULAR ROENTGEN SILHOUETTE

STUDIED BY MEANS OF ROENTGENOGRAMS OF THE CHESTS OF  
CADAVERS AFTER OPAQUE SOLUTIONS HAD BEEN  
INJECTED INTO THE LARGE VESSELS AND  
CHAMBERS OF THE HEART

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For a proper interpretation of roentgenograms of the chest an exact knowledge of the relations between the cardiac silhouette and the large vessels and chambers of the heart is necessary

Many interesting studies of this subject have been made and published by Keith<sup>1</sup> Dietlen, Roessler,<sup>2</sup> Parkinson,<sup>3</sup> Vaquez and Bordet,<sup>4</sup> Delherm and Thoyer Rozat and Laubry, Cottenot, Routier and Heim de Balsac,<sup>5</sup> but only the method followed by the last group has seemed to us quite convincing

With a similar procedure, we have tried to determine clearly the relations that normally exist between the contour of the cardiac shadow in roentgen films and the different chambers and large vessels of the heart

## ROENTGENOGRAPHIC METHOD

In Juarez Hospital, of Mexico City, sodium iodide solution was injected into the large vessels and the chambers of the hearts of several cadavers. Roentgenograms were then taken of the chests of these cadavers placed in the dorsoventral position and in oblique positions.

Roentgenogram 1 was taken of a cadaver in the dorsoventral position after 70 cc of a 50 per cent sodium iodide solution had been injected into the superior vena cava and the second and third costal cartilages resected. The distance between the tube and the film was 36 inches (91.5 cm), the x-ray apparatus was generating radiant energy at 65 kilovolts and 80 milliamperes.

Roentgenogram 2 was taken of a cadaver in the dorsoventral position in the same way as roentgenogram 1 and after the same preparation plus an injection of 35 cc of a 50 per cent sodium iodide solution into the ascending aorta.

Roentgenogram 3 was taken of the same cadaver as roentgenogram 2 with the chest in a 20 to 25 degree right anterior oblique position. The distance between the tube and the film was 36 inches, the time of exposure was one second and a half and the x-ray apparatus was generating radiant energy at 80 milliamperes and 70 kilovolts.

1 Keith, S. *Lancet* **1** 1466 (June 27) 1936

2 Roessler, H. *Clinical Roentgenology of the Cardiovascular System*. Anatomy-Physiology-Pathology-Experiments and Clinical Application, Springfield, Ill., Charles C Thomas, Publisher, 1937, *Atlas of Cardioroentgenology*, *ibid*, 1940. Golden, R. *Diagnostic Roentgenology*, New York, Thomas Nelson & Sons, 1937.

3 Parkinson, J. *Lancet* **1** 1337 (June 13), 1391 (June 20) 1936

4 Vaquez, H., and Bordet, E. *Radiologie du coeur et des vaisseaux de la base*, Paris, Masson & Cie, 1928.

5 Laubry, C., Cottenot, P., Routier, D., and Heim de Balsac, R. *J de radiol et d'electrol* **19** 193 (May), 561 (Oct) 1935, *Presse med* **102** 2071 (Dec 21) 1935, *Radiologie clinique du coeur et des gros vaisseaux*, Paris, Masson & Cie, 1939.

One can see that the superior left arch is formed by the aorta and that the straight segment placed above this arch is formed by the left carotid and the left subclavian artery

3 *Vessels, Right Chambers of the Heart and Aorta in Right Anterior Oblique Position (fig 3)*—One can easily recognize the superior vena cava and the ascend-

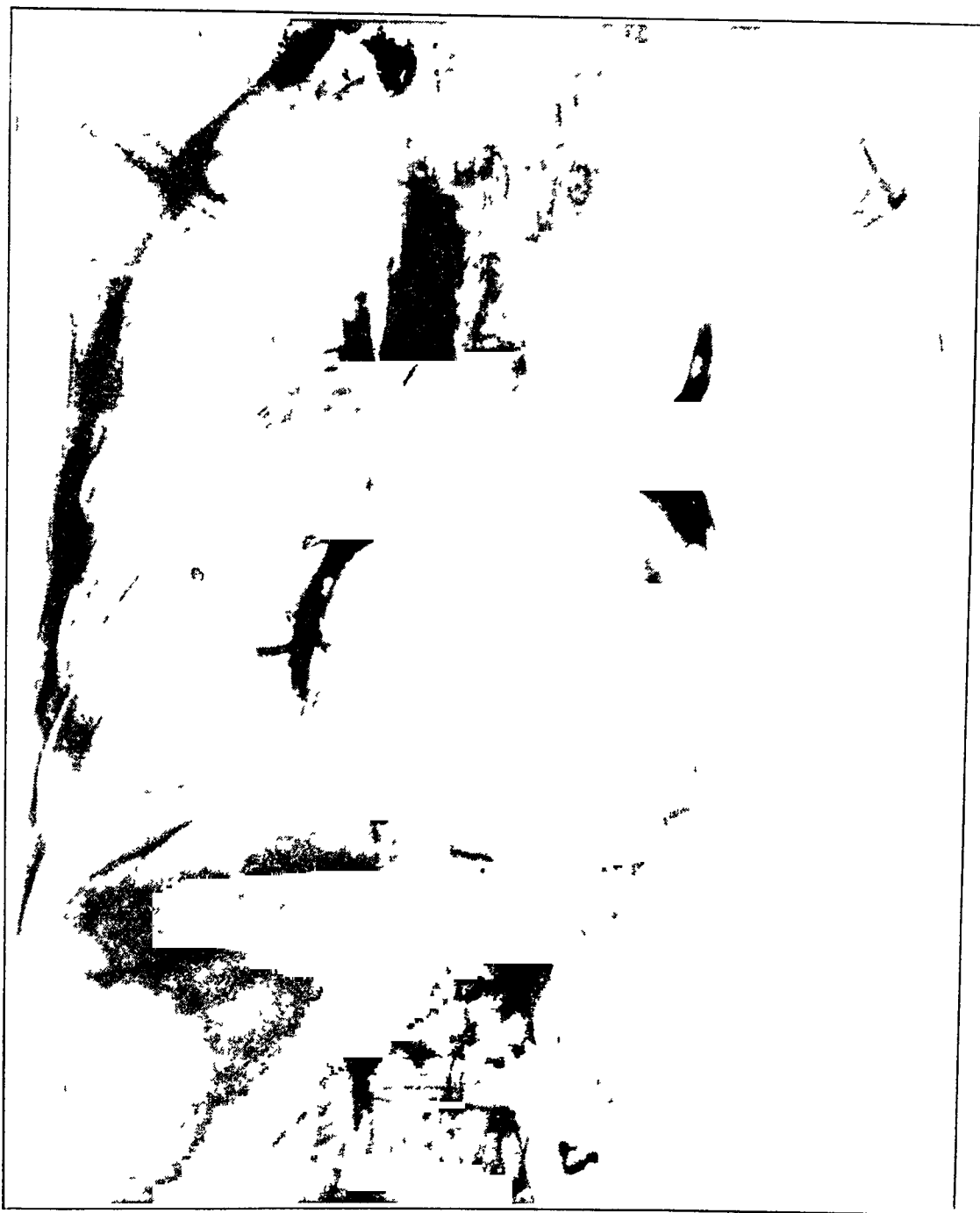


Fig 2—Vessels, right chambers of the heart and aorta of a cadaver in the dorsoventral position, taken under the same conditions as roentgenogram 1 except that an additional 35 cc of the opaque solution had been injected into the ascending aorta

ing aorta. The width of the former is 20 mm and that of the latter is 28 mm. One can recognize too, on account of the oblique direction of the vessel, a small portion of the descending aorta.

The contour of the shadow of the heart and large vessels in the right oblique position is formed on the spinal side by the superior vena cava in the upper part

On the upper part of the right side of the normal cardiac shadow one perceives a short, nearly vertical segment placed above the so-called right superior arch. It is obvious from this roentgenogram that this segment corresponds to the right innominate vein, placed behind the innominate artery.

Both innominate veins join to form the superior vena cava (80 mm long and 16 to 20 mm wide in this roentgenogram), which forms the right side of the contour of the cardiac shadow in that place called by some authors the superior right arch.

At the junction of the two upper thirds and the lower third of the so-called right superior arch is the hilar shadow as found on the normal roentgenogram of the chest. This is placed lower in the right lung than in the left. The site of this shadow is occupied in this roentgenogram by the ascending and descending branches of the right division of the pulmonary artery. The angle of division of these arteries is just 110 degrees.

One can see in this roentgenogram that the inferior right arch is formed by the right atrium and that the short straight segment placed below is the supra-diaphragmatic portion of the inferior vena cava as stated by Laubry, and that it is not formed by the hepatic veins as stated by Roessler. In the cadavers which we have dissected, the hepatic veins join the inferior vena cava below the diaphragm. In this roentgenogram, as well as in others we have taken, the hepatic veins join the inferior vena cava below the diaphragm.

The right ventricle is only partially filled on account of the valvular and papillary structures. The pulmonary artery, its right and left divisions and the ascending and descending branches of these were well filled with the opaque solution.

One can see in this roentgenogram that the middle arch in the left side of the cardiac silhouette is formed mainly by the pulmonary artery and by its left division. This fact must be emphasized.

One can see also that the right division of the pulmonary artery is longer than the left and that the left pulmonary hilus is higher than the right.

In this roentgenogram the pulmonary artery is 26 mm long and 21 mm wide, the right branch is 60 mm long and 25 mm wide. The apparent length of the left branch is 24 mm and the apparent width is 24 mm.

The cardiac shadow is in contact with the hepatic shadow for a distance of 70 mm and with the gastric clearness for a distance of 25 mm. The portion of the cardiac shadow in contact with the hepatic shadow is formed by the right ventricle for 50 mm and by the right atrium for 20 mm. The angle of division of the left pulmonary artery is 150 degrees and is placed on the upper part of the middle left arch, a little outward from the contour of the cardiac shadow. This is the place normally occupied by the left pulmonary hilar shadow.

*2 Vessels, Right Chambers of the Heart and Aorta in Dorsovenital Position (fig 2)*—The shadow obtained is quite similar to the former but the aorta is filled with the opaque solution. This filling is not complete in the ascending aorta.

One can clearly see that the ascending aorta is normally placed to the left of the superior vena cava and that normally the superior right arch of the cardiac silhouette is formed by the superior vena cava and not by the ascending aorta.

The left primitive carotid artery was filled with the opaque solution, showing that the intrathoracic portion of this artery is very long (60 mm). One can appreciate how difficult it would be to reach the aorta by palpation on the supra-sternal depression as some clinicians in our country pretend to do.

One can appreciate that the aorta, though in this roentgenogram visible in its three portions (ascending, transverse and descending), is normally visible only in its ascending portion, the transverse portion being superimposed on the tracheal clearness and the descending aorta on the shadow of the vertebrae

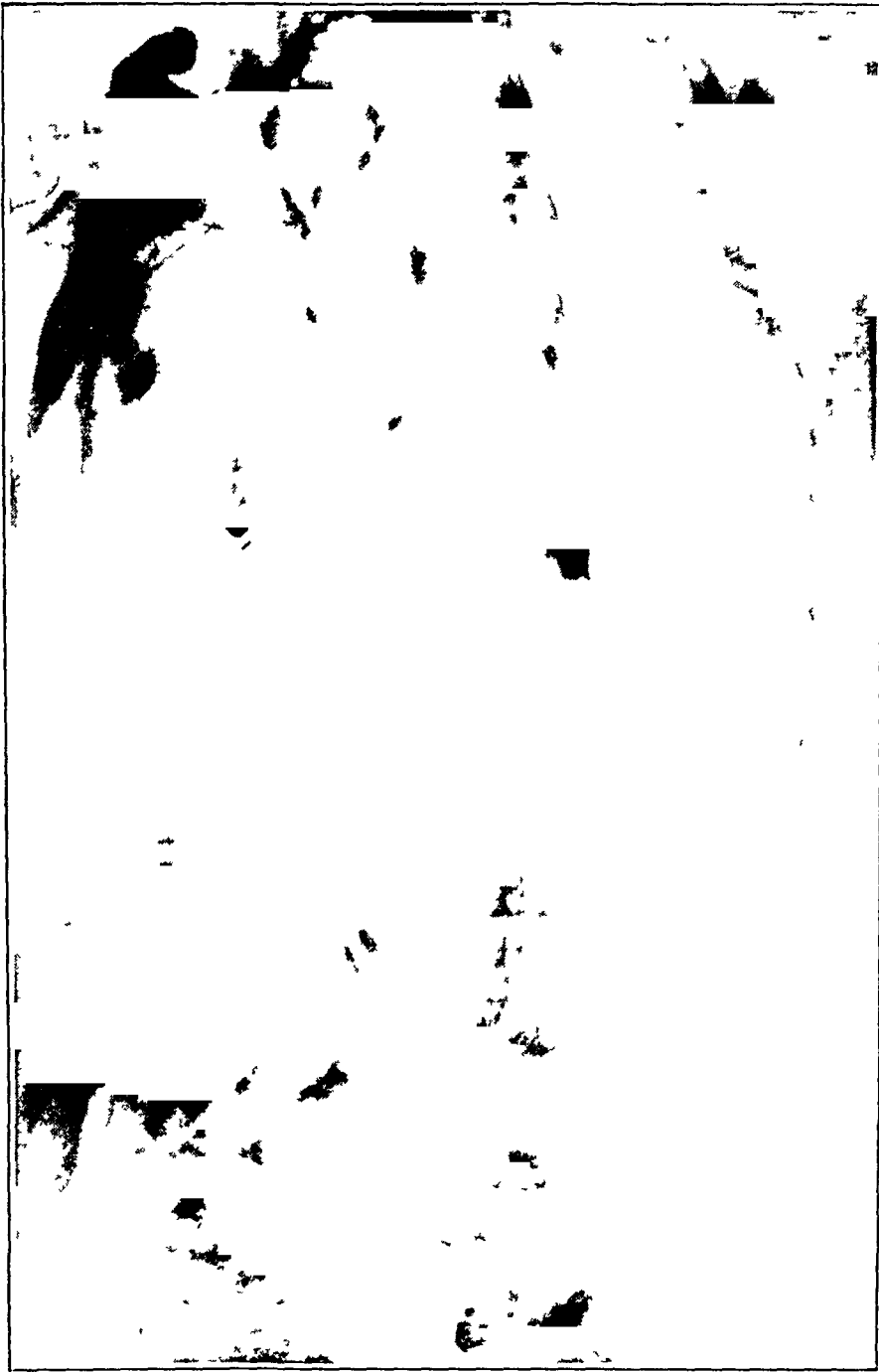


Fig 4—Vessels, right chambers of the heart and aorta in the cadaver shown in figures 2 and 3, taken with the chest in a left anterior oblique position

5 *Pulmonary Veins, Left Chambers of the Heart and Aorta in Dorsoventral Position (fig 5)*—The left atrium is normally placed behind the left ventricle. Consequently, only a small portion of it is visible in roentgenograms taken in the dorsoventral position, forming then the lower portion of the middle left arch.

Pulmonary veins are visible in the pulmonary field. They reach the right side of the cardiac silhouette on the upper part of the right inferior arch, below the pulmonary hilar shadow. They reach the left side of the contour of the cardiac

and by the right atrium in the lower part. On the other side the contour is formed from the cranial end downward by the pulmonary artery and its left division and by the left ventricle.

4 *Vessels, Right Chambers of the Heart and Aorta in Left Oblique Anterior Position (fig 4)*—The contour of the roentgen shadow in this position is formed

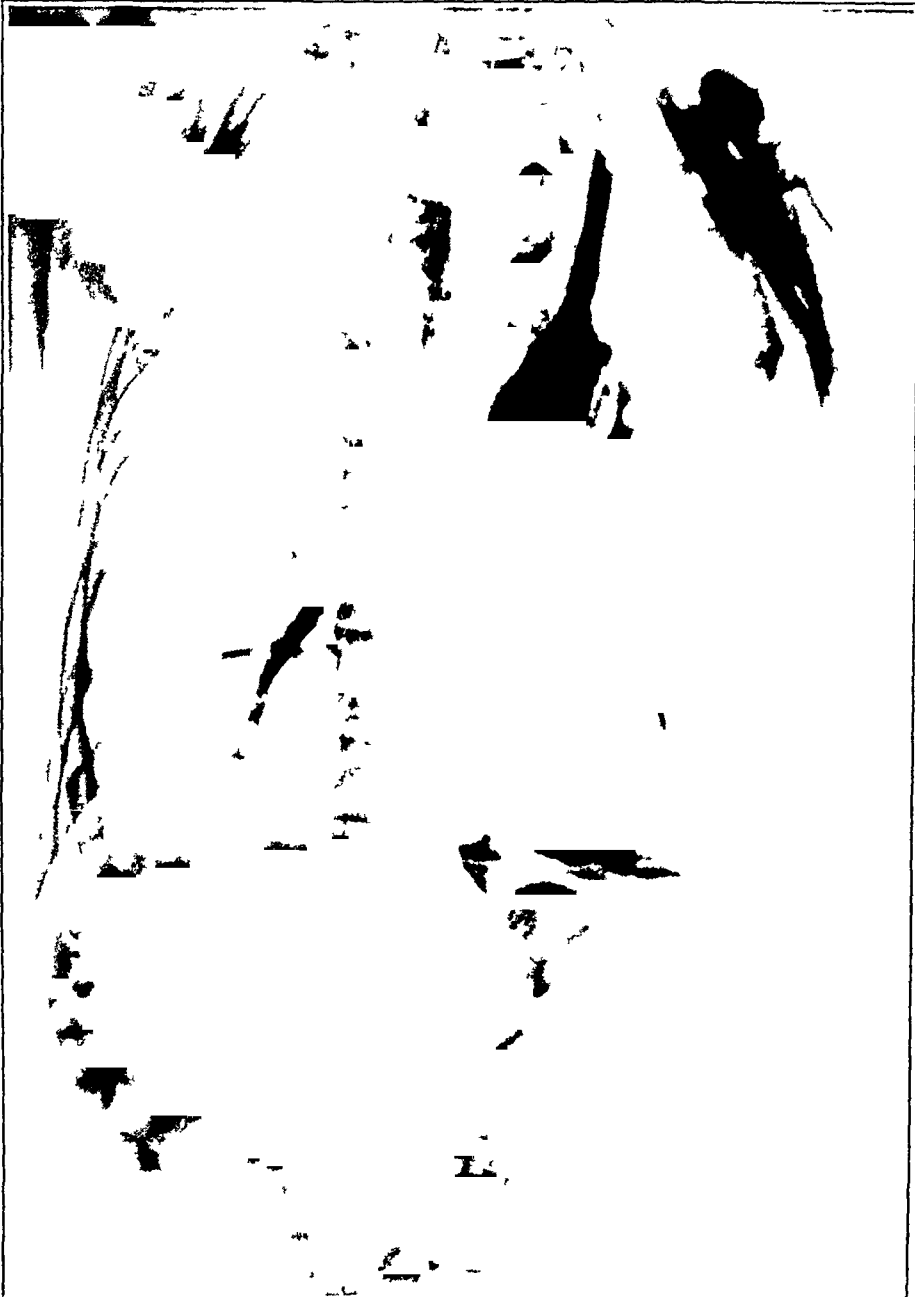


FIG 3—Vessels, right chambers of the heart and aorta in the cadaver shown in figure 2, taken with the chest in a right anterior oblique position.

on the ventral side by the superior vena cava in the upper part, by the ascending aorta in the middle portion and by the right ventricle in the lower part. On the dorsal side this contour is formed from the cranial end downward by the ascending aorta in the upper part, by the pulmonary artery in the middle portion and by the left atrium in the lower portion.

middle arch and that of the right is the lower part of the right superior arch, they are just the places of the branching of the left and right divisions of the pulmonary artery. The sites of the pulmonary veins are lower and correspond to the lower portion of the middle arch on the left and to the upper part of the inferior arch on the right.

The shadow of the pulmonary hilus in thoracic roentgenograms of normal subjects is therefore mainly *vascular* and even *arterial* in nature.

In roentgen kymograms taken with this field in view, one of us (Dr. Meneses Hoyos) and Dr. Gómez del Campo have always recognized the pulsation of the normal shadow of the pulmonary hilus, as shown in figure 6.

The middle arch on the left side of the cardiac shadow is formed mainly by the pulmonary artery *and its left division*.

The upper portion of the shadow located in the middle of the chest is formed neither by the aorta nor by the superior vena cava but by the innominate veins.

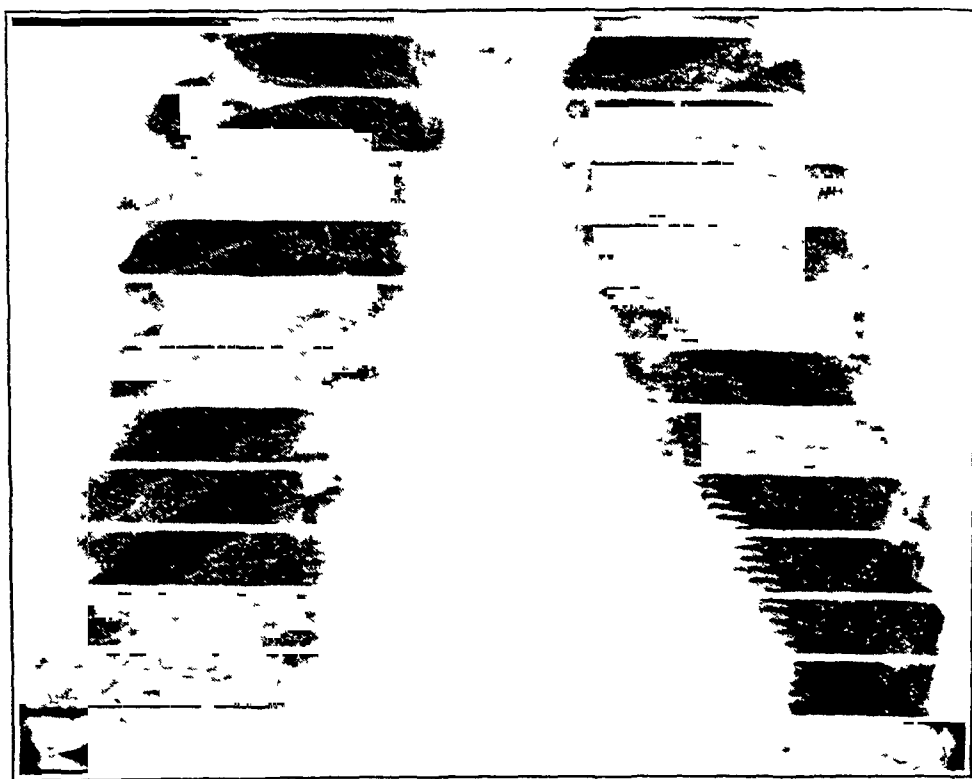


Fig. 6—Roentgen kymogram showing pulsation in the shadow of the pulmonary hilus (Dr. C. Gómez del Campo).

the innominate artery, the left carotid artery and the left subclavian artery. The short straight segment placed above the superior right arch is formed by the innominate vein covering the innominate artery. The short straight segment placed above the superior left arch is formed by the superposition of the left carotid and left subclavian arteries.

The distance between the aorta and the sternal fourchet varies widely in roentgenograms of normal persons but is always several centimeters and the aorta is not to be easily reached by palpation of the suprasternal depression.

#### SUMMARY AND CONCLUSIONS

The right side of the cardiac silhouette is formed from the cranial end downward by a short nearly vertical segment corresponding to the innominate vessels by the so-called right superior arch which normally corresponds to the superior vena



shadow on the lower part of the left middle arch, a little below the left pulmonary hilar shadow

One can thoroughly appreciate how great is the distance between the aortic arch and the sternal fouchet (38 mm in this roentgenogram) The apparent length of the ascending aorta is 55 mm, its diameter, 21 mm



Fig 5—Pulmonary veins, left chambers of the heart and aorta of a cadaver in the dorso-ventral position after injection of 35 cc of the opaque solution and resection of the second to seventh costal cartilages

#### COMMENT

In our roentgenograms some interesting facts become apparent that have not been enough emphasized in medical literature

The normal shadow of the pulmonary hilus in roentgenograms has the same place and the same form as the shadow of the right or the left division of the pulmonary artery at the site of its branching into an ascending and a descending artery The place of the left pulmonary hilar shadow is the upper part of the left

# SERUM CONCENTRATION AND RENAL CLEARANCE OF POTASSIUM IN SEVERE RENAL INSUFFICIENCY IN MAN

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The fact that during each day a normal person ingests by mouth and excretes in the urine and stool several grams of potassium had led to use of the expression "potassium balance." Since approximately 80 per cent of the output of potassium is excreted by the kidney, it has usually been assumed that the renal parenchyma possesses a special ability to excrete this ion. Indeed, the rapid renal excretion of potassium after the ingestion of a considerable amount of a potassium salt has been suggested as a reason for the nontoxic effect of potassium on the normal organism. If renal excretion is seriously impaired, as it may be in the presence of renal disease, it might be suspected that retention of potassium in the blood serum analogous to retention of other excretory constituents of the urine would occur. In animals with experimentally produced lesions of the kidneys, including bilateral nephrectomy, bilateral ligation of the ureters, bilateral chronic ionizing ray nephritis and intoxication with uranium and mercury bichloride, a progressive increase in the potassium concentration of the serum has been observed and has been regarded as a retention phenomenon<sup>1</sup>. Among human beings who have severe renal insufficiency, however, the values for serum potassium have not been found to be consistently increased. Among patients who have similar high degrees of retention of urea, the concentration of potassium in the serum may be increased in some and normal or even subnormal in others<sup>2</sup>. This rather considerable variation

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1 (a) Noguchi, I. Untersuchungen über den Mineralstoffwechsel in Nierenkranken, *Arch f exper Path u Pharmacol* **108** 73-77, 1925. (b) Beckmann, K., Bass, E., Durr, R., and Drosihn, G. Stoffwechsel und Blutveränderungen nach Nierenextirpation. Ionenverschiebungen und Saure-Blasengleichgewicht nach Nierenextirpation, *Ztschr f d ges exper Med* **51** 333-341, 1926. (c) Mark, R. E., and Kohl-Egger, E. Kalium-Kalziumspiegel im Serum nach Harnstoffgabe, *Zentralbl f inn Med* **48** 578-584 (June) 1927. (d) Hartwich, A., and Hessel, G. Der Kalium-, Calcium- und Kochsalzspiegel bei den verschiedenen Formen der experimentellerzeugten Uramie, *Klin Wchnschr* **7** 67-69 (Jan 8) 1928. (e) Nicholson W. M., and Schechter, A. J. Cardiac Arrhythmia After Bilateral Ureteral Ligation in the Dog, *Bull Johns Hopkins Hosp* **60** 346-357, 1937. (f) Bolliger, A., and Breh, F. Ueber die Mineralstoffveränderungen des Blutes bei experimenteller Nephritis, mit spezieller Berücksichtigung des Kalium-Kalziumspiegels im Serum, *Zentralbl f inn Med* **49** 825-831 (Sept) 1928.

2 (a) Meyers, V. C., and Short, J. J. The Potassium Content of Normal and Some Pathological Human Bloods, *J Biol Chem* **48** 83-92 (Sept.) 1921. (b) Zondek, H., Petow, H., and Siebert, W. Zur Frage der Funktionsstörung der Niere, *Klin Wchnschr* **1** 2172-2174 (Oct 28) 1922. (c) Wilkins, L., and Kramer, B. Studies on the Potassium Content of Human Serum, *Arch Int Med* **31** 916-922 (June) 1923. (d) Briggs, A. P. A Study of the Inorganic Elements of Blood Plasma, *J Biol Chem* **57** 351-357 (Sept) 1923.

(Footnote continued on next page)

cava, placed normally to the right of the ascending aorta, and by the inferior right arch, corresponding to the right atrium. The very short straight segment sometimes visible in the lower part of this silhouette is formed by the inferior vena cava. The suprahepatic veins were totally subdiaphragmatic in the cadavers we studied.

The left side of the cardiac silhouette is formed from the cranial end downward by a straight segment corresponding to the left carotid and left subclavian arteries, by the middle arch, corresponding on its upper portion to the *left division of the pulmonary artery*, on its middle portion to the pulmonary artery and on its lower portion to the left atrium, and by the inferior left arch, corresponding to the left ventricle.

In our roentgenograms the lower and outward pole of the shadow of the heart, usually called the apex, corresponds entirely to the left ventricle.

The shadows normally obtained at the sites of the pulmonary hili correspond to the branching of the right and the left division of the pulmonary artery. They are mainly *vascular* and even *arterial* in nature.

The silhouette of the heart and vessels in a right anterior oblique position is formed on the spinal side by the superior vena cava on its upper portion and by the right atrium on its lower portion. This same silhouette is formed on the ventral side from the cranial end downward by the ascending aorta (the innominate vessels and the left carotid and subclavian arteries being nearly transparent to roentgen rays), the pulmonary artery and its left division and the left ventricle.

The silhouette of the heart and large vessels in roentgenograms taken in a left anterior oblique position is formed on the ventral side by the superior vena cava on the upper portion, by the ascending aorta on the middle portion and by the right ventricle on the lower portion. On the spinal side it is formed on the upper part by the aorta, on the middle portion by the pulmonary artery and on the lower portion by the left atrium.

Normally, only the ascending portion of the aorta is visible on a roentgenogram taken in a left anterior oblique position, the transverse portion being superimposed on the tracheal clearness and the descending portion on the shadow of the vertebrae.

TABLE 2—*Clinical and Pathologic Observations*<sup>3</sup>

Case	Age, Yr	Sex	Edema, Grade 0 to 4	Hemo, globin, Gm per 100 Cc	Erythrocytes, Millions per Cu Mm	Blood Pressure, Mm Hg	Ocular Fundi	Died *	Diagnosis
4	42	M	0	8.0	2.90	190/240 110/170	Retinitis	D	Clinical diffuse arteriolar disease with hypertension group 3, myocardial degeneration with early failure Necropsy Diffuse arteriolar disease (hypertension) with superimposed glomerulitis
7	38	M	0.2	11.6 9.1	4.1 3.4	180/260 120/180	Retinitis papilledema	D	Clinical diffuse arteriolar disease with hypertension group 4, myocardial degeneration and decompensation, acute pericarditis edema of brain Necropsy arteriolar sclerotic atrophy of kidneys, fibrinous pericarditis
11	16	M	0.3	5.8 7.6	2.51 3.16	125/160 90/130	Retinitis	—	Clinical chronic glomerulonephritis, pulmonary congestion
14	25	F	0	5.3	1.50	175/245 125/160	Retinitis, papilledema disks anemic	D	Clinical chronic glomerulonephritis, diffuse arteriolar disease with hypertension group 4 Necropsy chronic glomerulonephritis
15	21	M	1.2	4.3	1.40	150/185 100/130	Acute angio spastic retin itis, anemia and edema of disks	D	Clinical chronic glomerulonephritis, pericarditis Necropsy chronic glomerulonephritis, fibrinous pericarditis, chronic tuberculosis of lungs and hilus nodes
18	41	M	0.1	6.6	3.00	180/220 110/160	Retinitis, papilledema	D	Clinical chronic glomerulonephritis, diffuse arteriolar disease with hypertension group 4, myocardial degeneration and decompensation, pulmonary edema, bronchopneumonia Necropsy granular atrophy of kidneys, hypertrophy of heart, bronchopneumonia
19	31	M	0	9.6	3.60	100/220 65/130	No retinitis	—†	Clinical chronic glomerulonephritis Necropsy advanced chronic glomerulonephritis with renal atrophy
24	64	F	0.1	6.2	2.95	140/230 70-105	No retinitis, no hemorrhages	—	Clinical chronic glomerulonephritis, chronic pyelonephritis(?), diffuse arteriolar disease with hypertension group 2, uremia
25	37	M	0	5.5	2.2	140/190 90/140	Anemia, no retinitis	D	Clinical chronic glomerulonephritis, severe anemia, myocardial degeneration with decompensation Necropsy chronic glomerulonephritis, uremia, fibrinous pericarditis
26	23	M	0.1	10.0 7.0	3.7 2.5	120/180 80/100	Anemia, no retinitis	D	Clinical chronic glomerulonephritis
27	16	F	0	6.3	2.10	140/180 95/125	Retinitis, anemia	—	Clinical chronic glomerulonephritis
30	25	M	0.1	12.3	2.87	120/170 70/100	Essentially normal	D	Clinical acute renal insufficiency (etiology? unknown toxic medication?), diabetes mellitus Necropsy Hypertrophy of kidneys (combined weight 627 Gm), hydropic degeneration of tubules and glomeruli, extensive sub-acute central necrosis of liver

\* Died in the hospital while under observation

† Died at home thirty two days after dismissal

in values for serum potassium among such patients seems to indicate that the concentration of serum potassium may be altered not only by impaired renal function but also by extrarenal factors. Of the latter the most obvious would be changes in the complicated ionic balances in the body fluids and tissue cells. To obtain additional information regarding this problem it seemed advisable, while a group of these patients were being observed in the hospital, to estimate repeatedly the concentration of potassium and certain other constituents in their blood serum and also to determine the volume of serum cleared of potassium by their urine during a given period. The following report is the result of clinical and chemical investigations of 33 patients who had definite renal insufficiency. Pathologic study also was carried out on 14 of them.

SELECTION OF PATIENTS

The 33 patients included in this study were of two groups: (1) patients with chronic diffuse nephritis and (2) patients with subacute nephritis and passive congestion (table 1). The first group was comprised of 29 patients who were selected because they were suffering from chronic disease of the kidneys and definite renal dysfunction. The primary diagnosis for 8

TABLE 1—Distribution by Condition Thirty-Three Cases of Definite Renal Insufficiency

Condition Present	Cases	
	Total Number	Numerical Designation
Chronic Diffuse Nephritis		
Chronic nephrosclerosis *	8	1 through 8
Chronic pyelonephritis	2	9 and 10
Chronic glomerulonephritis (no potassium salt given)	16	11 through 26
Chronic glomerulonephritis (potassium salt given)	3	27 through 29
Total	29	1 through 29
Subacute Nephritis and Passive Congestion		
Indeterminate subacute process	1	30
Subacute bilateral thrombosis	1	31
Passive congestion †	2	32 and 33
Total	4	30 through 33

\* In case 6 potassium chloride was injected once intravenously.  
† In case 32, 15 Gm. of potassium nitrate was given by mouth.

of these patients was chronic diffuse arteriolar disease with marked involvement of the kidneys, or chronic nephrosclerosis, for 19, chronic glomerulonephritis, and for 2, chronic pyelonephritis. Renal insufficiency was extreme in 26 of these patients, the severity of renal dysfunction was indicated by greatly increased concentrations of urea and creatinine in the blood. The remaining 3 patients, who had chronic glomerulonephritis (cases 27, 28 and 29 in table 1), were included because to each of them a potassium salt was administered. They did not have such severe renal insufficiency as did the other 26 patients, and in 2 of them (cases 28 and 29) features of chronic lipid nephrosis were present.

In the second group of 4 patients (cases 30 through 33 in table 1), rapid progressive renal insufficiency developed while the patients were under observation. The cause in 1 of them was obscure, in the second arterial thrombosis with multiple infarcts of both kidneys occurred, and in the remaining 2 there was marked congestion of the kidneys secondary to myocardial failure.

(e) Nelken, L., and Steinitz, H. Ueber den Gehalt des Blutserums an Calcium und Kalium bei Nierenkrankheiten, *Ztschr. f. klin. Med.* **103**: 317-341, 1926. (f) Salvesen, H. A. Variations in the Serum Electrolytes in Diseases of Renal Origin with Special Reference to the Cause of Renal Acidosis, *Acta med. Scandinav.* **69**: 126-186, 1928. (g) Green, C. H., Wakefield, E. G., Power, M. H., and Keith, N. M. The Electrolyte Distribution and the Acid-Base Equilibrium in the Serum in Cases of Nephritis and Nephritic Acidosis, *Biochem. J.* **26**: 1377-1382, 1932. (h) Hoffman, W. S., and Jacobs, H. R. D. The Partition of Potassium Between the Serum and Corpuscles in Health and Disease, *J. Lab. & Clin. Med.* **19**: 633-644 (March) 1934. (i) Atchley, D. W., Loeb, R. F., Benedict, E. M., and Palmer, W. W. Physical and Chemical Studies of Human Blood Serum. II. Study of Twenty-Nine Cases of Nephritis, *Arch. Int. Med.* **31**: 611-615 (April) 1923.

women, and their ages varied from 16 to 64. Moderate to severe anemia usually was present. Observations made in case 15 (table 2) revealed the most severe anemia, the concentration of hemoglobin decreasing to 4.3 Gm per hundred cubic centimeters and the erythrocyte count to 1,400,000 per cubic millimeter. Definite hypertension was present in 28 patients and absent in 2, whereas in the 3 remaining

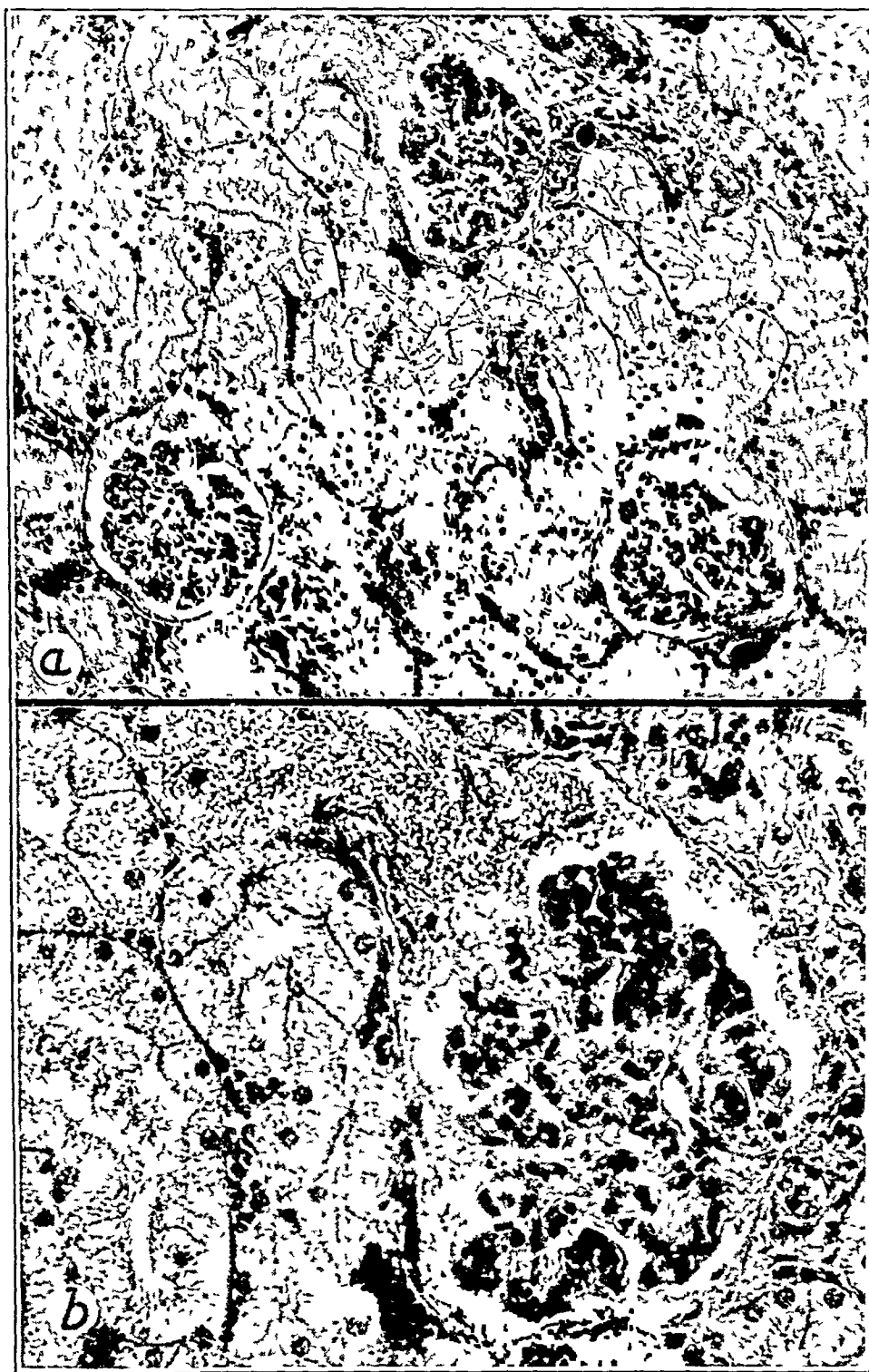


Fig 2 (case 30) —Sections from a kidney (hematoxylin and eosin, *a*,  $\times 125$ , *b*,  $\times 300$ ). There is hydropic degeneration of the tubules, the cells having a pale, foamy, edematous appearance. Many tubules contain casts of albuminous material and some contain pus. In occasional tubules there is calcium material with more advanced degenerative changes. Glomeruli and arterioles appear to be fairly normal.

patients the blood pressure usually was normal but on a few occasions increased to abnormal values.

## OBSERVATIONS

*Clinical and Pathologic Observations*—A summary of the significant clinical data obtained in 12 of the series of 33 cases and the pertinent pathologic observations in 8 of them are given in table 2<sup>3</sup> Seventeen patients were men and 16 were

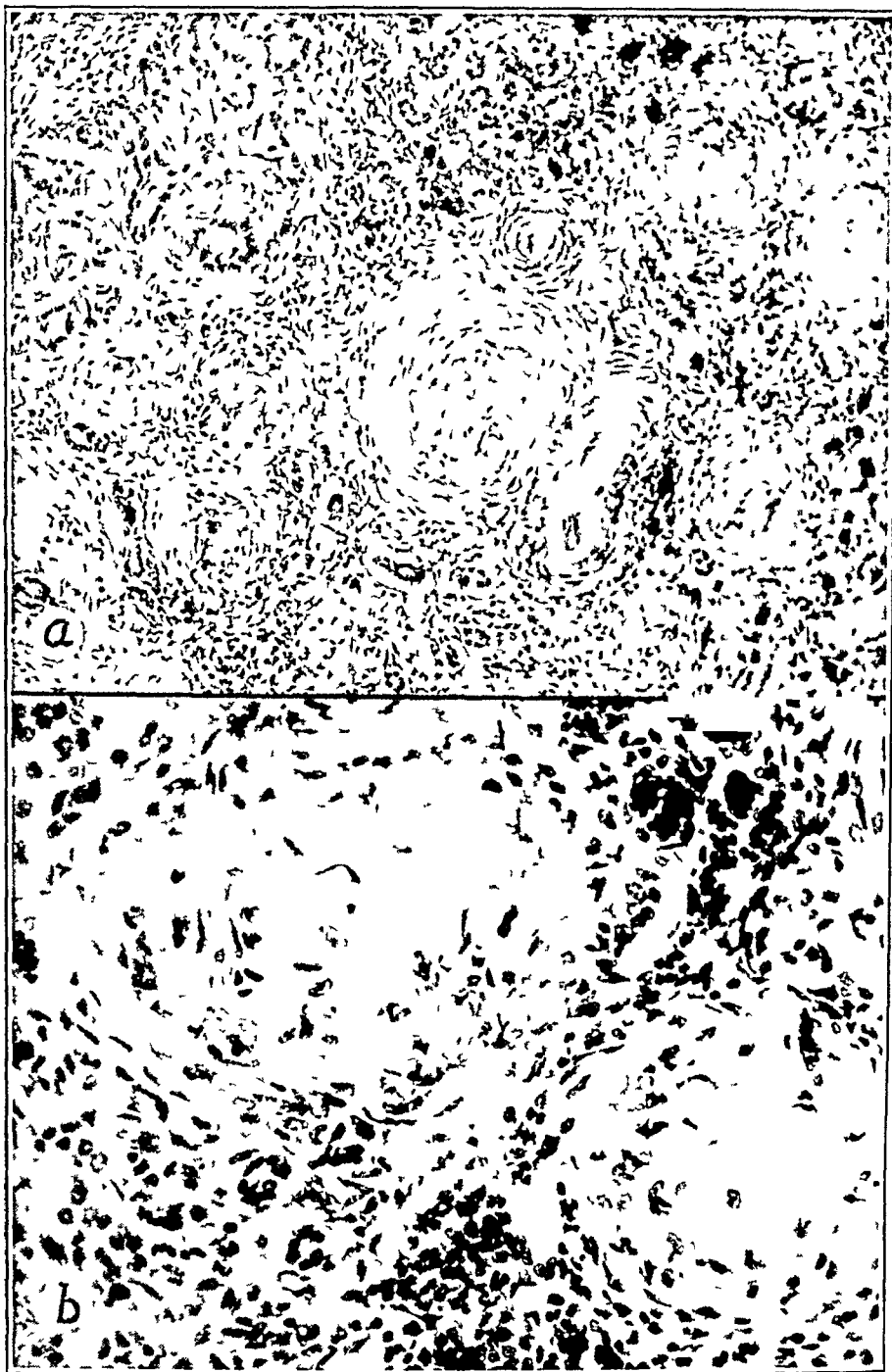


Fig 1 (case 14) —Sections from a kidney (hematoxylin and eosin, *a*,  $\times 100$ , *b*,  $\times 320$ ) There are numerous hyalinized glomeruli and atrophy of the tubules. An increase in interstitial connective tissue and collections of lymphocytes can be seen. The vessels appear to be fairly normal, but in other sections (not shown) of this kidney pronounced arteriosclerosis with almost complete obliteration of the lumens could be seen. Arteriosclerosis also was marked.

3 Observations in all 33 cases were extremely valuable, but for purposes of conservation of space the data for only 12 appear in extenso in tables 2 and 3.

ment of this patient afforded a good opportunity for study of the effects of the ingestion of potassium salts on renal function and on the concentration of potassium in the serum

TABLE 3—*Chemical Studies of the Blood*<sup>3</sup>

Case	Hos- pital Day	Blood				Serum						Plasma			
		Hg, Gm per 100 Cc	Mg per 100 Cc		Gm per 100 Cc		Mg per 100 Cc				Potas- sium Ratio	Mg per 100 Cc		CO <sub>2</sub> Com- bining Power, Vol %	
			Urea	Creat- inine	Pro- tein	Albu- min	Potas- sium	Sod- ium	Cal- cium	Phos- phorus		Sul- fate	Chlor- ide (as Chlorine)		Choles- terol
4	5 14 18†	8.0	188 274	11.2 16.0	5.8	4.1	19.2 25.8	308 310			15.3 22.8*	0.0624 0.0830	327 351	228	47.5 47.5*
7	1 20 23 35 45 58†	11.6	116 420* 396* 396 358	5.4 10.4* 10.4* 8.8 6.4			22.2 25.4 25.0 23.9	325	8.5		15.7 22.9*	0.0683	349* 353*		57.9 33.4* 39.0*
11	3 7 9 14 17 25	5.8	286 346 346 273 267 266	16.8 13.6 16.0 13.6 14.6 13.6	6.1 5.9 5.7	3.6 3.5 3.1	19.6 22.2 19.5 21.0 18.7 22.2	307 284 296 319 313 313		4.3 4.6 4.6 4.3 3.9	9.6 14.7	0.0638 0.0784 0.0659 0.0658 0.0597 0.0709	327 264 276 270 313		24.0 27.0 27.0 72.0 61.0 .
14	3 4 7†	5.3	214	12.0	5.3		17.6 18.2	305	6.3		20.5	0.0597	342 330		32.8
15	2 4 8 9†	4.3	220 266* 392	13.2 15.2* 18.4	4.9	1.9	27.8 40.9	290	.		20.8	0.1410	373	181	27.6
18	1 2 3†	6.6	332 396	16.0 18.4	5.9	4.3	20.7 22.3 34.2	290 296			41.0 49.0 59.4	0.0714 0.1157	280		46.6 44.9
19	19 20	9.6	353* 356	18.4*			20.3 17.8	308			30.7*	0.0659	317*		35.3*
24	3 6 10 13 15 16	6.2	90 81 90 110 130 138	4.4 4.2 5.7 5.7 4.5			30.1 31.2 35.1 38.8 34.6	296		5.2	12.7 10.8 13.5	0.1185	343		52.0
25	3 6 13 16† 20 28 30†	5.5	276 252 258	20.0 18.4 18.4			20.9 27.7 34.2 31.0 33.5	305			24.2	0.1016	314 309	175	52.2 50.4 39.0 27.7
26	2 8 14 28 40 50 55†	10.0	94 154 248 327 394	3.4 3.8 5.2 7.0	4.3 3.3	2.1	34.1 33.7 31.0 25.7 27.4	288 273	6.8	8.8	9.9	0.1076 0.1004	388 338 316 306	277 370	35.3 29.6 32.4 36.2
27§	4 6 7	6.3	124 118	7.6 8.4	5.1 5.3	3.4 3.5	32.9 31.0 37.3						413		38.0
30	2 5 6†	12.3	258 288	10.0 15.2	4.9	3.5	19.7	296			38.6	0.0666	317	273	49.4 34.3

\* These values were not obtained on the same specimen of blood as the corresponding values of potassium, but were for other specimens obtained within forty eight hours

† Day of death

‡ On the sixteenth day the patient received 300 cc of citrated blood by transfusion. The concentration of potassium in blood serum immediately after transfusion was 34.1 mg per hundred cubic centimeters as compared with 34.2 mg in specimen withdrawn prior to transfusion

§ This patient ingested a potassium salt during observation in the hospital. Details of the amount taken are given in table 4

Pathologic studies<sup>4</sup> in 10 cases of the group in which the condition present clinically appeared to be chronic renal disease revealed diffuse chronic lesions

4 Dr A. H. Baggenstoss, of the section on pathologic anatomy of the Mayo Clinic, made the pathologic observations



The course of the illness after examination in this series of patients emphasizes the serious nature of the renal lesions. Seventeen patients died while they were under observation in the hospital, and 15 died later, but within eight months of their dismissal. A single patient (case 29) is alive thirty-two months after dis-

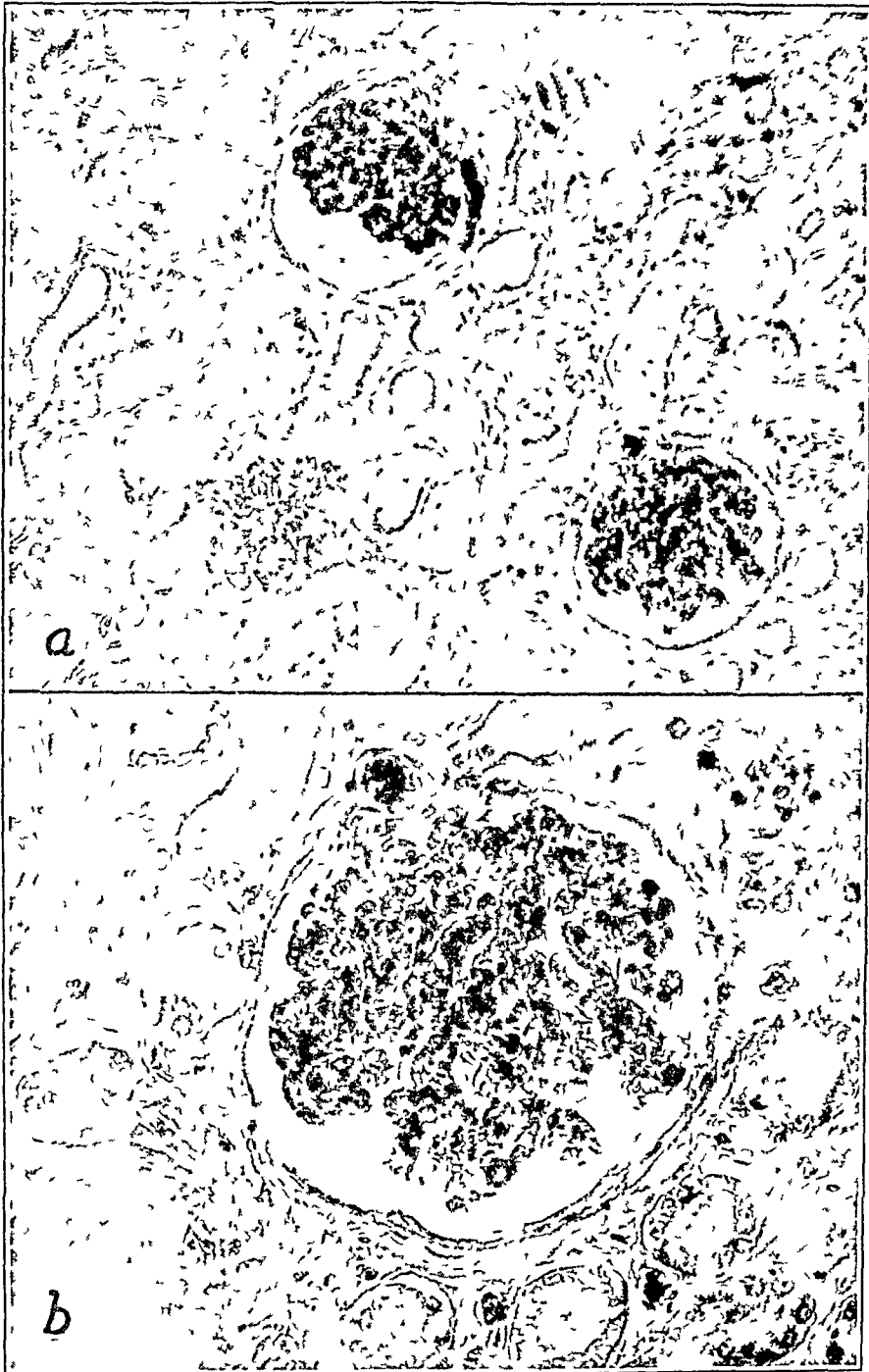


Fig 3 (case 32) —Sections from a kidney (hematoxylin and eosin, *a*,  $\times 125$ , *b*,  $\times 300$ ). Marked congestion and occasional focal atrophy of tubules (chronic infarction). Evidence of severe passive congestion. Old pyelonephritic scar. Little foci of atrophy of tubules, with fibrosis and interstitial lymphocytes. Glomeruli congested, but glomerulitis not present. Deposits of calcium and casts in tubules. No arteriolar sclerosis of any degree.

missal. This patient had renal dysfunction which was much less severe than that of any other in the series, and the data are included because potassium salts had been administered for their diuretic action. Therefore conditions during the treat-

blood. These mean concentrations were 242, 122 and 272 mg per hundred cubic centimeters respectively. Some degree of acidosis was present in 30 of 33 patients, as indicated by a reduction in the carbon dioxide-combining power of the plasma. This reduction varied considerably, it was slight in some patients and extreme in others. Hypochloremia was present in many patients, and the concentration of sodium in the serum also was often considerably reduced. Our finding that the concentration of both the chloride in the plasma and the sodium in the serum was frequently reduced in cases of severe renal insufficiency is in agreement with previous experience.

The concentration of phosphorus in the serum was determined for 10 patients and was found to be increased in all, the actual values were 5.0 to 17.3 mg per hundred cubic centimeters. The content of calcium in the serum was estimated for 13 patients, it varied from 3.9 to 10.2 mg per hundred cubic centimeters. Symptoms of tetany were not present, even in patients who had very low concentrations of calcium in the serum. There was, however, no correlation found between increases of phosphorus or decreases of calcium and the increment of potassium in our series of patients. The cholesterol content of the plasma was definitely increased to more than 300 mg per hundred cubic centimeters in 5 patients (cases 8, 17, 26, 28 and 29), and in all 5 edema and hypoproteinemia also were present.

Analysis of our data with regard to the concentration of potassium in the blood serum reveals some very interesting observations. The concentration varied from 12.8 to 40.9 mg per hundred cubic centimeters, as compared with a normal range of 17 to 21.3 mg.<sup>7</sup> Such an increased variation over normal seems difficult to explain. However, on further examination it is evident that patients with persistent severe renal insufficiency who have a subnormal or normal value for serum potassium on a single occasion will later often, although not invariably, be found to have an abnormally high concentration of potassium. Actual results show that for 14 of the 33 patients a single value was within the normal range, whereas on the other hand 24 of the 33 patients had at least one value which was more than the maximal normal, 21.3 mg per hundred cubic centimeters. In 16, or 66 per cent, of the latter 24 patients the serum potassium reached a concentration of more than 25 mg. These results give ample evidence that in the presence of uremia, repeated determinations of the concentration of potassium in the serum often will reveal an abnormal increase, whereas a single estimation may not.<sup>8</sup>

In cases 24, 26 and 27 interesting results are disclosed. The initial concentrations of potassium in the serum were abnormally high, 30.1, 33.7 and 32.9 mg per hundred cubic centimeters, although the urea and creatinine in the blood had not increased to extremely high levels, the values for urea being 81, 154 and 124 mg and those for creatinine 4.4, 3.4 and 7.6 mg respectively (table 3). Several investigators have previously noted a high value for potassium in the serum of a single

7 This was the range obtained in a series of normal persons by Furey (Furey, E. D. Normal Variations in Proteins and Certain Inorganic Elements of the Blood Serum, Proc Staff Meet, Mayo Clin **13** 730-732 [Nov 16] 1938).

8 In diabetes mellitus (Rathery, F., and Bertoliatti, J. Variations du taux du potassium dans le sang et diabète sucré, Compt rend Soc de biol **116** 1346-1349, 1934. McQuarrie, I., Thompson, W. H., and Anderson, J. A. Effects of Excessive Ingestion of Sodium and Potassium Salts on Carbohydrate Metabolism and Blood Pressure in Diabetic Children, J Nutrition **11** 77-101 [Jan] 1936), in tetany,<sup>2c</sup> in wound shock,<sup>25</sup> in certain allergic states (Rusk, H. A., Weichselbaum, T. E., and Somogyi, M., with the technical assistance of Simms, E. Changes in Serum Potassium in Certain Allergic States, J A M A **112** 2395-2398 [June 10] 1939. Hoffman and Jacobs<sup>2h</sup>), in burns and in some infections accompanied by fever increases in serum potassium to more than normal have been reported. In the present series of cases we believe these conditions have been excluded with the exception of fever.

throughout the kidneys (fig 1 case 14) On the other hand, in the group of 4 cases in which rapid progressive renal insufficiency developed necropsy revealed subacute renal lesions in 2 (fig 2, case 30) and severe congestion in 2 (fig 3, case 32) The adrenal glands were examined in 13 cases in which necropsy was performed, because of the known relationship between the hormones of the adrenal cortex and potassium metabolism Histologic study did not reveal any distinctly abnormal condition, in a few of the cases of diffuse arteriolar disease the walls of some of the arterioles of the capsule and of the gland itself were distinctly thickened Rabinowitch<sup>5</sup> in 1925 suggested a possible relationship between a high potassium sodium ratio in the blood serum and dilatation of the heart In 5 of his patients with a high potassium sodium ratio in the serum he observed pronounced dilatation of the heart at necropsy Our experience in 3 cases was somewhat different (tables 1, 2 and 3) In case 9, with the concentration of potassium in the serum increased

TABLE 4—*Effect of Potassium Salts on the Concentration of Potassium in the Blood Serum of Five Patients*

Case	Hospital Day	How Given	Amount Gm	Period of Administration, Days *	Serum Potassium, Mg per 100 Cc	Blood Urea, Mg per 100 Cc	Diagnosis
6	17	Intravenously	7.2 KCl in 900 cc solution		18.9	226	Chronic nephrosclerosis
	18						
	20				22.4	315	
27	6	Per os	5.0 KHCO <sub>3</sub>		31.0		Chronic glomerulonephritis
	7				37.3	118	
28	111	Per os	46 KNO <sub>3</sub>	11	22.6		Chronic glomerulonephritis
	122				33.1	114	
	152				23.1	76	
29	4	Per os	40 KNO <sub>3</sub> 27 KNO <sub>3</sub> 10 KCl	5	24.4		Chronic glomerulonephritis
	9				21.7		
	14				26.8		
	19				27.7	60	
	26				25.0	52	
32	5	Per os	15 KNO <sub>3</sub>	3			Passive congestion of kidney
	9				24.2	106	

\* Period of administration completed on the evening of the previous day

to 34 mg per hundred cubic centimeters and the potassium sodium ratio to 0.1062, there was no evidence of cardiac dilatation However, in cases 15 and 18 both the concentration of potassium in the serum and the potassium sodium ratio were distinctly increased and moderate dilatation of the left ventricle was observed at necropsy

*Observations in Chemical Studies of the Blood*—Results of chemical studies of the blood<sup>6</sup> of certain of our 33 patients are listed in tables 3 and 4 It is apparent that severe renal insufficiency and retention of certain metabolites in the blood were the rule The abnormally high retention of metabolites in 29 patients is strikingly shown by the mean concentration of urea, creatinine and sulfate in the

5 Rabinowitch, I. M. On the Relative Proportions of Sodium, Potassium, Calcium and Magnesium in Blood Plasma in Renal Disease, *J Biol Chem* 62:667-673 (Jan.) 1925

6 The blood obtained from patients in this study was withdrawn from a vein in the elbow, in the morning, before the ingestion of food

intoxication with potassium (fig 6, case 15)<sup>11</sup> These investigators expressed the beliefs that the abnormal results seen in electrocardiograms obtained in their experiments were caused by the increase in the concentration of potassium in the serum and that death of an animal in the presence of such experimentally produced intoxication is due to cardiac failure, which in turn is brought about by the high concentration of potassium in the serum We cannot entirely exclude the possibility that the early electrocardiographic changes noted in case 15 might be due to acute pericarditis which was present at this time, but we think the evidence is strongly suggestive that the later changes were due to potassium intoxication If these changes in the electrocardiogram developed as a result of the high concentration of potassium in the circulating plasma, 40.9 mg per hundred cubic centimeters, or 10.4 milliequivalents, we believe these tracings are the first to indicate the occurrence of such intoxication in a patient suffering from chronic nephritis and uremia In this connection Cushny<sup>12</sup> made a very interesting statement in 1917, when he said that a concentration of potassium in blood plasma "in anything over about 50 mg per cent is highly poisonous to the heart" The evidence in case 15 that potas-

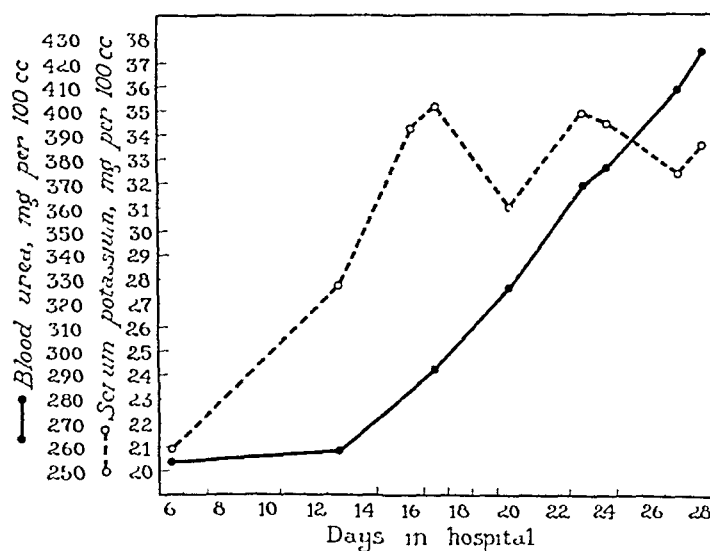


Fig 5 (case 25) —Contrast between the concentration of urea in the whole blood and of potassium in the serum of a patient with terminal uremia On the sixth hospital day the value for urea was 252 mg (five times normal) and that for potassium was 20.9 mg, a normal figure From that day until death there was a distinct increase in the concentrations of both urea and potassium

sium might be playing a causative role in the production of the toxemia in uremia revives a viewpoint hinted at by Meissner<sup>13</sup> in 1866, suggested by Voit<sup>14</sup> in 1868 and discussed at length by Feltz and Ritter<sup>15</sup> in 1881

11 In case 32 the electrocardiogram showed on the seventh hospital day an intraventricular conduction defect with a QRS complex of 0.16 second On the patient's first day in the hospital the QRS complex was of normal duration, and it seems possible that the change might be attributed to an increase in the concentration of potassium in the serum, as has been suggested in case 15 (table 4) Further support to this suggestion was the absence of any demonstrable myocardial lesions on histologic examination Dr H B Burchell interpreted these electrocardiographic tracings

12 Cushny, A R The Secretion of Urine, London, Longmans, Green & Co, 1917

13 Meissner, G Bericht über Versuche die Uramie betreffend, Ztschr f rat Med 26 225-249, 1866

14 Voit, C Ueber das Verhalten des Kreatins, Kreatinins und Harnstoffs im Thierkörper, Ztschr f Biol 4 77-162, 1868

15 Feltz, V, and Ritter, E De l'urémie expérimentale, Paris, Berges, Levraut & Cie, 1881

similar patient In our 3 patients (cases 24, 26 and 27) the serum potassium was sustained at a high level, although the patients continued to excrete a considerable volume of urine As renal insufficiency increased in case 26 from the fourteenth to the fortieth day in the hospital, there was a gradual decrease in the concentration of potassium in the serum from 33.7 to 25.7 mg (fig 4, case 26)

The results in cases 4, 15, 18 and 25, in which chronic nephritis was present, emphasize that terminal renal failure, with oliguria in cases 15 and 18 but with a considerable output of urine in case 4, may be accompanied by an increase in serum potassium (fig 5, case 25) Bolliger and Breh<sup>11</sup> reported similar results in chronic experimental nephritis produced by roentgen rays In case 15, during terminal renal failure when acute pericarditis developed and the concentration of serum

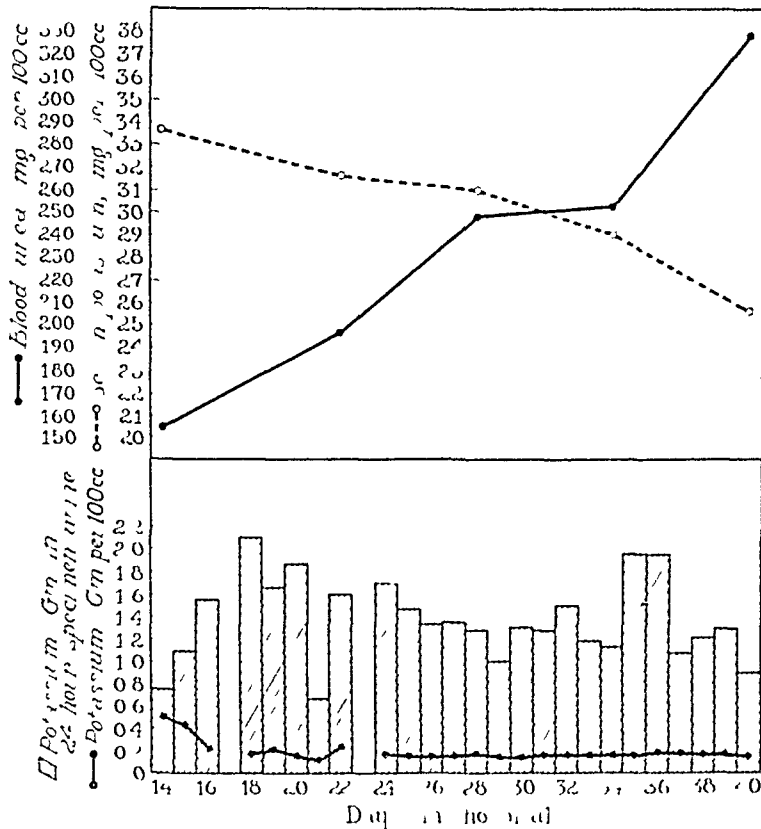


Fig 4 (case 26)—Contrast between the concentration of urea in the whole blood and the concentration of potassium in the serum On the fourteenth day, with an increase in urea to 154 mg (three times normal), the value for potassium was relatively high (33.7 mg) As the content of urea steadily increased to reach 327 mg on the fortieth day, the content of potassium decreased, to 25.7 mg Early in this period the concentration of potassium in the urine gradually decreased and then remained at a fixed value, the total output of potassium in the urine remained fairly constant throughout the entire period of twenty-six days Note that on the twenty-second day the concentration of potassium in the serum was 31.7 mg and the concentration in the urine was 207 mg, six times greater than that in the serum

potassium was increasing rapidly, electrocardiograms were made on several occasions These tracings revealed some very definite progressive changes, which were similar to those reported by Hoff, Smith and Winkler<sup>10</sup> in experimentally produced

9 Footnote deleted on proof  
10 Hoff, H E, Smith, P K, and Winkler, A W The Cause of Death in Experimental Anuria, J Clin Investigation 20 607-624 (Nov) 1941

concentration of potassium in the serum did not. The patient had had marked oliguria for four days previous to admission, and during three of the days during which he was under observation in the hospital the daily twenty-four hour output of urine totaled 150 cc, none and 15 cc respectively. In spite of this pronounced oliguria and anuria, the concentration of potassium in the serum on the morning of the day before death was 197 mg per hundred cubic centimeters. This result is perhaps comparable to that obtained in one experiment on a series of dogs rendered anuric by mercury bichloride in the study by Hoff, Smith and Winkler<sup>10</sup>

The low initial concentration of potassium in the serum in case 31 is of especial interest. This patient, a physician, had been vomiting frequently for several weeks before his admission, and he himself suggested the possibility of an intrinsic gastric lesion. No such lesion was present. The low intake of food and loss of potassium in the vomitus probably played an important role in his having a subnormal concentration of serum potassium, 12.8 mg per hundred cubic centimeters, for at that time his renal function was not markedly disturbed. With the subsequent rapid development of oliguria and severe renal insufficiency due to arterial thrombosis in the kidneys, the concentration of urea in the blood rose to 390 mg and the serum potassium to a normal concentration, of 17.9 mg<sup>18</sup>. Snapper<sup>19</sup> reported a similar low concentration of serum potassium in a case of acute mercury poisoning with renal insufficiency.

A decided improvement in renal function took place in a single instance in the present series (case 10) while the patient was under observation. The improvement in renal excretion was accompanied with a distinct decrease in the concentration of serum potassium from an abnormally high (27.3 mg) to a normal level (20.4 mg)<sup>20</sup>. Scholtz reported a similar experience in 1 of his cases of secondary contracted kidney. Since this sequence of events occurred in our case 10 and in that of Scholtz, in both of which chronic diffuse nephritis was present, it seems reasonable to suppose that it may happen more frequently in the receding phase of severe acute renal insufficiency. A somewhat different result occurred in case 21. Some improvement in renal function, as indicated by a decrease of 60 mg in the concentration of blood urea, was accompanied not by a decrease but by a slight increase in serum potassium.

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18 Rosenberg, E. F., Keith, N. M., and Wagener, H. P. Diffuse Arterial Disease with Hypertension. Two Unusual Cases of Contrasting Types, *Arch Int Med* **62** 461-481 (Sept) 1938.

19 Snapper, I. *Chinese Lessons to Western Medicine*, New York, Interscience Publishers, Inc., 1941.

20 Treatment during this period in case 10 consisted of ingestion of a diet containing approximately 2,000 calories, 60 Gm of protein and 3 to 5 Gm of sodium chloride. The intake of fluid averaged 2,000 to 3,000 cc, 1,000 cc of this daily intake of fluid often was injected intravenously and contained 100 Gm of dextrose or 9 Gm of sodium chloride, or both substances in these amounts. After these therapeutic measures polyuria, improvement in renal function and a decrease in serum potassium took place. Similar treatment was carried out in many other cases of this series without demonstrable effect on the concentration of potassium in the blood serum. In addition, blood was transfused to several of our patients. In case 15, in which severe uremia was present, blood was transfused on the third hospital day. Estimation of the potassium content of the serum next morning revealed a high value, of 27.8 mg per hundred cubic centimeters. Four days later it had increased to 40.9 mg. We do not think that the transfused blood had a causal relation to the increase in serum potassium, because in a subsequent case the values for serum potassium before and after transfusion of blood were identical. In neither this patient's case (case 15) nor in others did we make a systematic study of the effect of transfusion on the constituents of the blood. Our available data failed to reveal any constant change in the potassium content of serum due to the transfusion of blood.

Rapid renal failure with oliguria occurred in cases 30, 32 and 33, in which the renal pathologic process proved to be either a subacute or a congestive state. In cases 32 and 33 the concentration of potassium in the serum was distinctly increased to 34.2 and 27.1 mg in 100 cc respectively and renal failure was due to congestion of the kidneys. Two previous groups of observers have made similar observations, that is, the concentration of potassium in the serum may become distinctly increased in patients who are suffering from myocardial decompensation with congestion of the kidneys. In 1922 Olmer, Payan and Berthier<sup>16</sup> reported on 3 such patients. Later, in 1932, Scholtz<sup>17</sup> especially mentioned 3 similar cases and commented on the absence of a renal pathologic process other than the passive congestion. In case 30 (tables 2 and 3), however, rapid renal failure and oliguria did develop, but a high

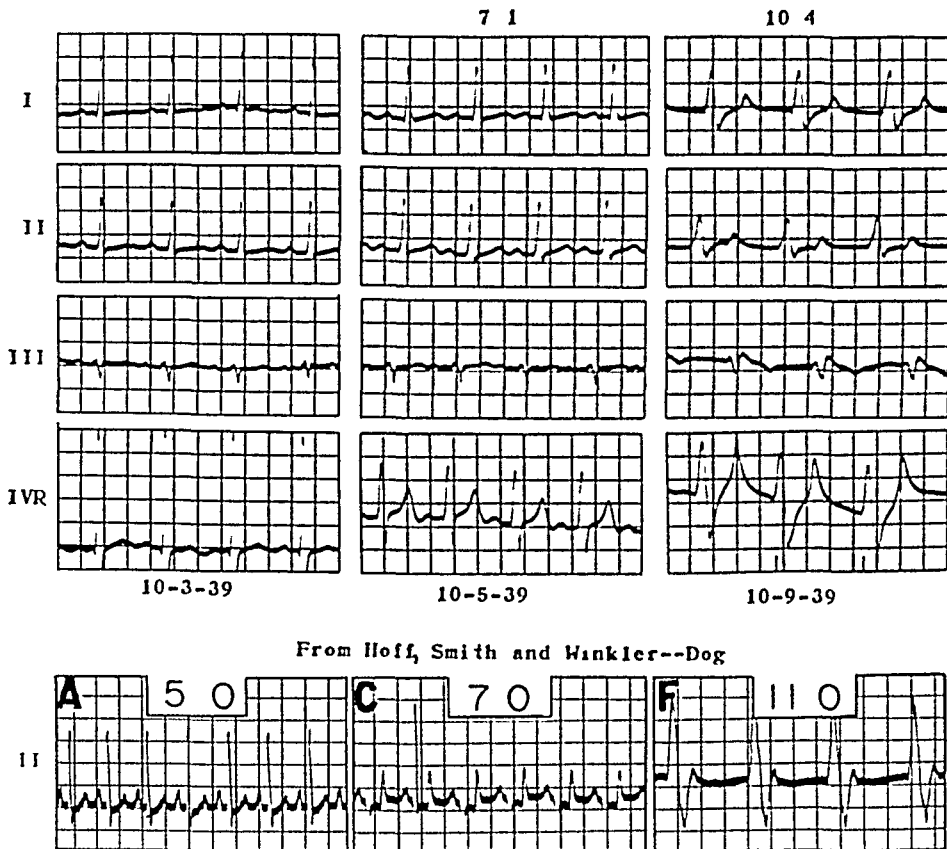


Fig 6—Electrocardiograms made in case 15, in which fatal uremia with pericarditis developed and in which the value for serum potassium was high, compared with the electrocardiogram of a dog poisoned by potassium chloride. At the time the first tracing was made pericarditis was present, but it had no characteristic representation in the electrocardiogram. The changes in the T waves in the second tracing, particularly in the fourth lead, are similar to those which we have obtained after the administration of potassium to man. The last tracing, without P waves and with an intraventricular conduction defect, is most unusual, and we were impressed by its similarity to the tracings published by Hoff, Smith and Winkler<sup>10</sup> in their report on experimental intoxication with potassium (p 608). Above the second and third tracings made in our case are given the potassium content of the serum in milliequivalents, as also noted, below, in the three tracings of the dog.

16 Olmer, D., Payan, L., and Berthier, J. Le potassium du serum sanguin dans l'insuffisance renale, *Compt rend Soc de biol* **87** 867-869 (Sept 15) 1922.

17 Scholtz, H. G. Ueber den Calcium- und Kaliumgehalt im Blutserum und die Ultrafilterbarkeit dieser Minerale beim Niereninsuffizienz, *Deutsches Arch f klin Med* **172** 472-482, 1932.

(not included in this series) who had a similar type of chronic glomerulonephritis and a similar grade of renal insufficiency was given 5 Gm of potassium bicarbonate by mouth within ninety minutes the concentration of potassium increased from a control level of 267 mg to 371 mg. In both these patients the tolerance for potassium was distinctly reduced. Zwemer and Truszkowski<sup>26</sup> observed in Addison's disease a similar reduction in the tolerance for potassium. The effect of the administration of a potassium salt by vein was observed in a single patient (case 6 in table 4). In this patient on the morning of the seventeenth hospital day, the concentration of urea in the blood was increased to 336 mg, whereas the value for potassium in the serum was normal, or 189 mg. During the evening of the eighteenth hospital day the patient received 900 cc of an 0.8 per cent solution of

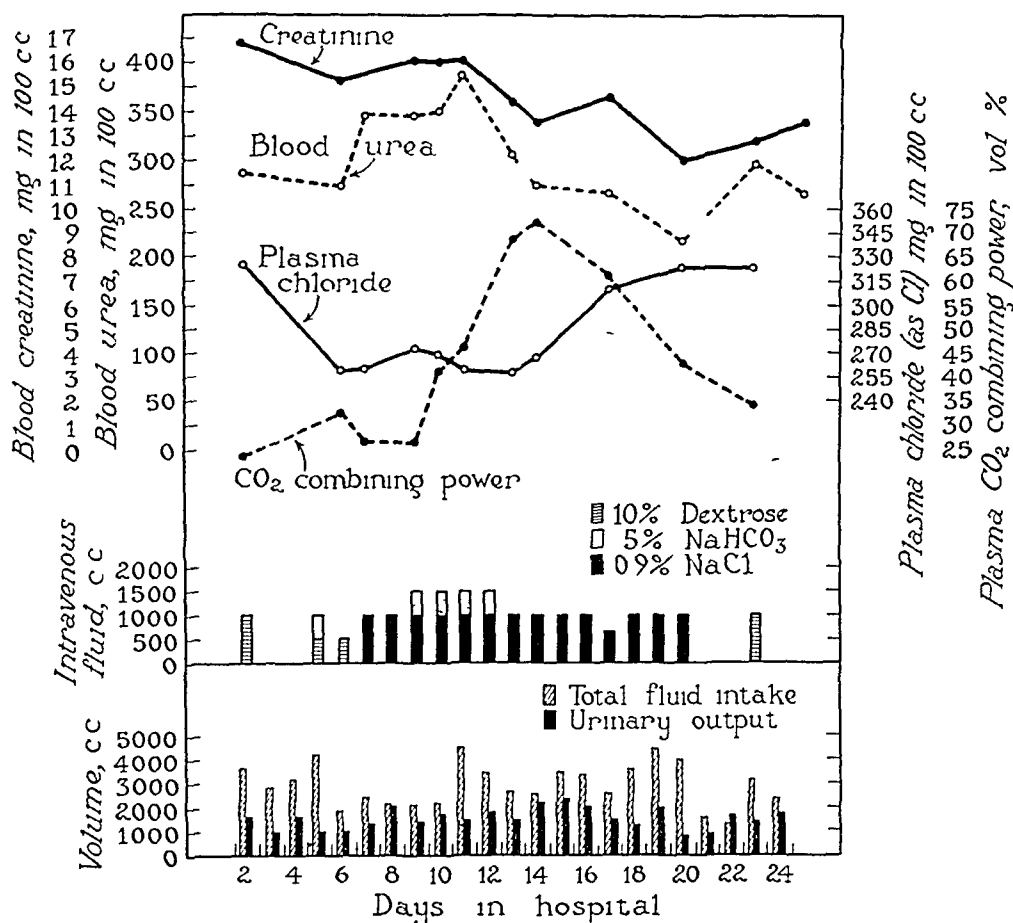


Fig 7 (case 11) —Variations in the concentration of urea and creatinine in whole blood and of chloride and carbon dioxide-combining power in plasma. Intake of fluid, including solutions injected intravenously, and output of urine are shown.

potassium chloride (7.2 Gm of potassium chloride) intravenously. On the morning of the twentieth day, thirty-six hours after the injection, the value for potassium in the serum was 22.4 mg per hundred cubic centimeters. Thus, we found that the intravenous administration of a considerable amount of potassium chloride to a patient who has serious renal insufficiency does not necessarily lead to a sustained high level of the potassium in the serum.

*Comparative Chemical Observations in the Blood and Urine*—Quantitative estimations were made of certain constituents in the urine and blood in case 11.

26 Zwemer, R. L., and Truszkowski, R. Factors Affecting Human Potassium Tolerance, *Proc Soc Exper Biol & Med* 35:424-426 (Dec) 1936.



Rabinowitch has briefly discussed the potassium sodium ratio in serum from patients with cardiorenal disease. The mean normal ratio as recorded by Macallum<sup>21</sup> is 0.0611. Rabinowitch found an elevation to more than 0.0700 in only 5 of 14 cases, in all of which the blood urea nitrogen was more than 90 mg per hundred cubic centimeters (a blood urea concentration of more than 190 mg). The ratio was calculated in 26 cases in our series. Normal ratios<sup>22</sup> were present at some time in 11 cases, and increased ratios were observed in 18. It is apparent that there was a tendency toward increased potassium sodium ratios in many of our cases, but there are definite exceptions when individual cases are considered. It should also be pointed out that the normal ratio was found in cases in which there was a normal concentration of potassium in the serum and the increased ratio was found in those in which there was an abnormally high concentration of potassium in the serum. Therefore this ratio appears to vary directly according to the concentration of potassium present.

The ingestion of a potassium salt may cause a distinct temporary increase in serum potassium, both in the normal and in the sick person, as previously noted by Thomson,<sup>23</sup> Keith and Binger<sup>24</sup> and others<sup>25</sup>. Such was the succession of events in cases 27, 28 and 29 (table 4). The ingestion of 15 Gm of potassium nitrate (case 32) four days before the high concentration of potassium was observed in the serum probably played a very minor role in causing an increase to 34.2 mg per hundred cubic centimeters (table 4). A brief summary of the history and course in the hospital in case 28 follows.

A man 45 years old was admitted to the clinic on Sept. 28, 1933, complaining of swelling of the feet, scrotum, abdomen and face. He said the condition had been present for four weeks. For six years he had noted intermittent nausea and vomiting within two hours after eating but had had no pain. He had noted occasional headache and increased fatigue, and for the four weeks preceding admission there had been increasing edema, decreased urinary output and albuminuria. Vision was normal. Physical examination revealed edema, grade 3, of the feet, legs and scrotum, suggestive early ascites and a puffy appearance of the face. Urinalysis disclosed a specific gravity of 1.007 to 1.013, albuminuria of grade 1 to 2, pyuria of grade 1 to 2, no sugar, no erythrocytes and no casts. Thoracentesis on the right side was necessary on two occasions, and abdominal paracentesis was necessary on six occasions. The patient was dismissed on March 19, 1934 (one hundred and seventy-first hospital day).

Studies of potassium in this case showed that during the eleven day interval between the determinations of values of serum potassium 22.6 and 33.1 mg per hundred cubic centimeters the patient received a total of 46 Gm of potassium nitrate. During the thirty day interval between the determinations of serum potassium concentrations of 33.1 and 23.1 mg the patient received a total of 66 Gm of potassium nitrate, of which only 12 Gm was given in the twenty days immediately preceding determination of the value of 23.1 mg.

The increase of potassium in the serum in case 27 was particularly striking. Ninety minutes after the ingestion of 5 Gm of potassium bicarbonate the concentration in the serum increased to 37.3 mg from a previous level of 31 mg per hundred cubic centimeters. We have since observed that when a young woman

<sup>21</sup> Macallum, A. B. The Ancient Factors in the Relations Between Blood Plasma and the Kidneys, *Tr. Coll. Physicians, Philadelphia* **39**: 286-299, 1917.

<sup>22</sup> The normal range was calculated by taking the quotients resulting from dividing the minimal and maximal normal serum potassium values by the maximal and minimal normal serum sodium values respectively, for example, 17 divided by 359 = 0.047 and 21.3 by 315 = 0.068.

<sup>23</sup> Thomson, W. A. R. The Effect of Potassium on the Heart in Man, *Brit. Heart J.* **1**: 269-282 (Oct.) 1939.

<sup>24</sup> Keith, N. M., and Binger, M. W. Diuretic Action of Potassium Salts, *J. A. M. A.* **105**: 1584-1590 (Nov. 16) 1935.

<sup>25</sup> Scudder, J. Shock. Blood Studies as a Guide to Therapy, Philadelphia, J. B. Lippincott Company, 1940.

the concentration of potassium in the serum 21, 187 and 222 mg In 1921 Kiamer and Tisdall in the original description of their micromethod for determining potassium in the serum reported increases in the concentration of potassium in

TABLE 5—*Certain Constituents of Urine in Case 11, Collection of Urine for Twenty-Four Hour Period*

Hospital Day	Volume Cc	Specific Gravity	Inorganic Sulfate		Urea		Creatinine		Nonprotein Nitrogen		Total Protein *		Potassium		Comment
			Gm per 100 Cc	Total Gm	Gm per 100 Cc	Total Gm	Gm per 100 Cc	Total Gm	Gm per 100 Cc	Total Gm	Gm per 100 Cc	Total Gm	Gm per 100 Cc	Total Gm	
14	555†	1 011	0 038	0 21	0 58	3 20	0 031	0 17	0 31	1 70	0 27	1 50	0 017	0 09	
17	1,390	1 010	0 036	0 50	0 48	6 70	0 033	0 46	0 29	4 00	0 23	3 20	0 013	0 18	
18	1,170	1 010	0 036	0 42	0 54	6 30	0 034	0 40	0 30	3 50	0 33	3 90	0 010	0 12	
19	1,910	1 010	0 036	0 69	0 55	10 50	0 034	0 65	0 31	5 90	0 33	6 30	0 012	0 23	
20	860	1 010	0 043	0 37	0 54	4 60	0 034	0 29	0 32	2 80	0 35	3 00	0 015	0 13	Acute pulmonary edema developed, temp 98.6 F, 1,000 cc 0.9% NaCl i v
21	860	1 011	0 053	0 46	0 55	4 70	0 038	0 33	0 33	2 80	0 43	3 70	0 063	0 58	Pulmonary edema with bloody sputum, temp 102 F
22	1,510	1 010	0 031	0 47	0 57	8 60	0 039	0 59	0 37	5 60	0 53	8 00	0 043	0 65	Condition improved, temp 100 F, less orthopnea
23	1,400	1 010	0 053	0 74	0 55	7 70	0 034	0 48	0 33	4 60	0 47	6 60	0 050	0 70	Much improved, temp 98 F
24‡	1,850	1 010	0 055	1 00	0 52	9 60	0 036	0 67	0 33	6 10	0 35	6 50	0 045	0 83	Temp 98 F

\* Estimated by subtracting the nonprotein nitrogen from the total nitrogen and multiplying the result by 6.25. The nonprotein nitrogen was estimated after precipitating the protein with Folin's tungstic acid reagent.

† Single catheterized specimen only, incomplete twenty four hour collection.

‡ The patient was discharged on the twenty fifth hospital day, and death occurred at his home six days later.

TABLE 6—*Comparison of the Concentration of Certain Constituents of Blood and Urine*

Case	Hospital Day	Mg per 100 Cc					
		Urea		Creatinine		Potassium	
		Blood	Urine	Blood	Urine	Serum	Urine
7	23	396		10.4		25.4	150*
	45	358	865	6.4		23.9	149*
11	14	273	580	13.6	31	21.0	17*
	17	267	480	14.6	33	18.7	13
	20	216	540	12.0	34		15
	21		550		38		63
	22		570		39		43
	23	294	550	12.8	34		50
	24		520		36	22.2	45

\* Single specimen of urine obtained by catheter.

the serum of children who had various infectious diseases and associated fever Zwemer, Sims and Coggeshall<sup>27</sup> also observed an increase in the value of serum potassium during the period of chills and fever in patients suffering from malaria.

In case 7 (table 6) simultaneous determinations of the concentration of potassium in the blood serum and urine were made on two occasions. On the

<sup>27</sup> Zwemer, R. L., Sims, E. A. H., and Coggeshall, L. T. Plasma Potassium Level During Malaria Infection in Monkeys and Man, *Am J Trop Med* 20: 687-701 (Sept) 1940.

These data afforded us a unique opportunity to compare, for example, the concentrations of urea and creatinine in whole blood and potassium in blood serum with the concentrations of these substances in the urine (figs 7 and 8, tables 5 and 6) On the fourteenth day of observation in the hospital blood was withdrawn from a vein in the arm and urine was obtained from the bladder by catheter a few minutes later The concentrations of urea and creatinine in the urine were approximately twice those in the blood, whereas the values for potassium were almost identical 17 mg per hundred cubic centimeters in the urine and 21 mg in the blood serum This observation in regard to potassium suggested a process of renal filtration On

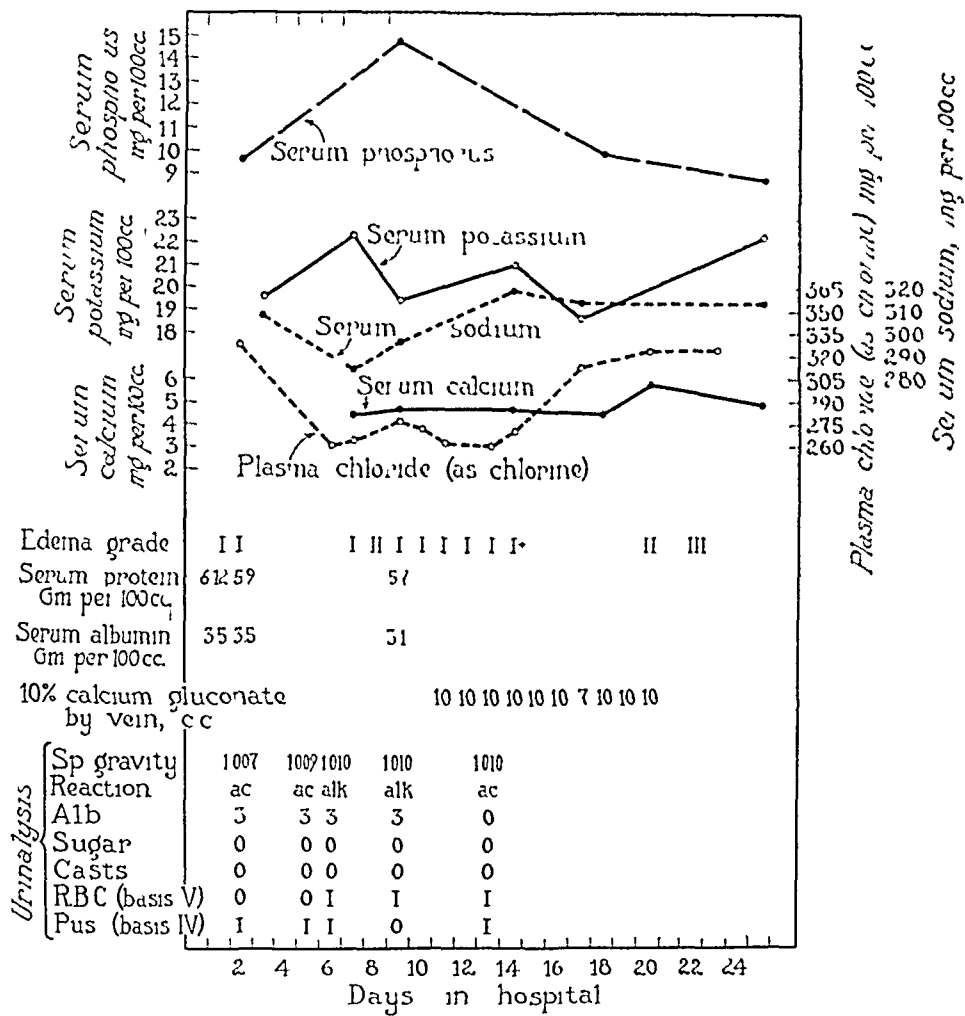


Fig 8 (case 11)—Variations in the concentration of certain electrolytes, protein and albumin in the serum Grade of edema and results of routine urinalysis are depicted

the other hand, similar data obtained from the twentieth to the twenty-fourth day offered evidence that this same diseased kidney could a few days later concentrate the potassium in the serum several times and thus readily bring about excretion of it During the latter period there was an increased formation and renal excretion of urea, creatinine, sulfate and potassium, most probably due to breakdown of protein, since pulmonary edema developed at this time and the patient's temperature increased to 102 F (38.8 C) However, the concentration and output of potassium in the urine increased relatively to a greater degree than those of the other three urinary constituents It is of interest that this rather striking increase in the excretion of potassium by the kidney was accompanied by only slight changes in

were very noticeable (fig 9, case 7). Almost identical observations in regard to the excretion of potassium were obtained in the study of case 26. In this case even when the concentration of potassium in the serum reached 31.7 mg the concentration in the urine was 207 mg, or six times greater than that in the serum (fig 4, twenty-second day).

The continued functional ability of a seriously damaged kidney to excrete and concentrate potassium and urea is of further interest in view of some results which we obtained in the study of the blood and urine of 3 patients, not included in the present series, who had uremia and who died within two and a half to thirty hours after specimens of blood and urine were withdrawn simultaneously for determinations of urea. Blood was withdrawn by needle from a vein in the elbow, and urine was secured by catheter from the bladder. The concentrations of urea in the blood plasma were 369, 519 and 627 mg per hundred cubic centimeters, and the corresponding concentrations in the urine were 626, 785, and 952 mg. These observations concerning urea and those noted previously concerning potassium reveal that even at the very termination in a case of chronic diffuse nephritis the renal parenchyma may be capable of concentrating the urea and potassium of the circulating plasma.

*Comparison of the Clearance by the Kidney of Potassium and of Urea*—Our experience in cases 11 and 7 in regard to the excretion of potassium by the kidney led us to determine the actual clearance of the blood serum of potassium into the urine and to compare its clearance with that of urea during a short period, of approximately one hour<sup>28</sup>. The clearances were determined in the early morning before breakfast. The results observed in ten clearance periods, in 8 of our cases, are listed in table 7. The most striking result is that urea clearance was markedly reduced in every case, whereas clearance of potassium was reduced below the minimal normal value in only 2 instances (cases 10 and 19). In case 19 renal dysfunction was pronounced and the concentration of potassium in the urine was the lowest observed in the cases in which studies of clearance were made, in fact, the concentration of potassium was approximately isotonic with that in the serum. A similar observation was made in case 11 on the fourteenth hospital day (tables 5 and 6). In the second instance of decreased potassium clearance (case 10) the clearance was reduced to 5 cc, the minimal normal value being 6 cc. However, when the test was repeated seven days later, the clearance had increased to 7 cc. Thus, in only a single instance (case 19) was the clearance of potassium found to be distinctly less than normal, this result most likely is to be explained by the histopathologic changes observed in this case. There was marked destruction of the renal parenchyma (fig 10). It was pointed out previously that the oral ingestion of 5 Gm of potassium bicarbonate in case 27 had led to a rapid increase in the

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28 Since pus cells frequently were present in the urinary sediment in our cases, and since these cells contain intracellular potassium, the question arose as to whether the presence of such cells in the urine augmented the actual quantity of potassium excreted by the kidneys. The urine was especially examined in 5 cases with regard to this point. In case 9 the concentration of potassium in the urine was very low, yet the sediment contained large numbers of leukocytes. In case 27 clearance was estimated twice, in one specimen of urine there were no leukocytes, in the other 20 to 50 cells to a field were found with the high power lens. Yet the concentrations of potassium in the two specimens were practically identical. We then analyzed a sample of well shaken urine and also a sample of the same urine obtained from the upper portion of the tube after rapid centrifuging for several minutes. The concentration of potassium was the same in the two samples. The results of this experiment, carried out on urine from 5 patients, were similar. There were never more than a few erythrocytes in the sediment, so their presence would not have altered the concentration of potassium. The foregoing evidence is convincing that the concentration of potassium in the urine was not increased by the presence of leukocytes.

twenty-third hospital day a specimen of urine (260 cc obtained by catheter) contained 150 mg of potassium per hundred cubic centimeters, whereas the value for potassium in the serum was 25.4 mg. Similar observations were made on the forty-fifth hospital day (table 6), or two weeks before the patient died. These

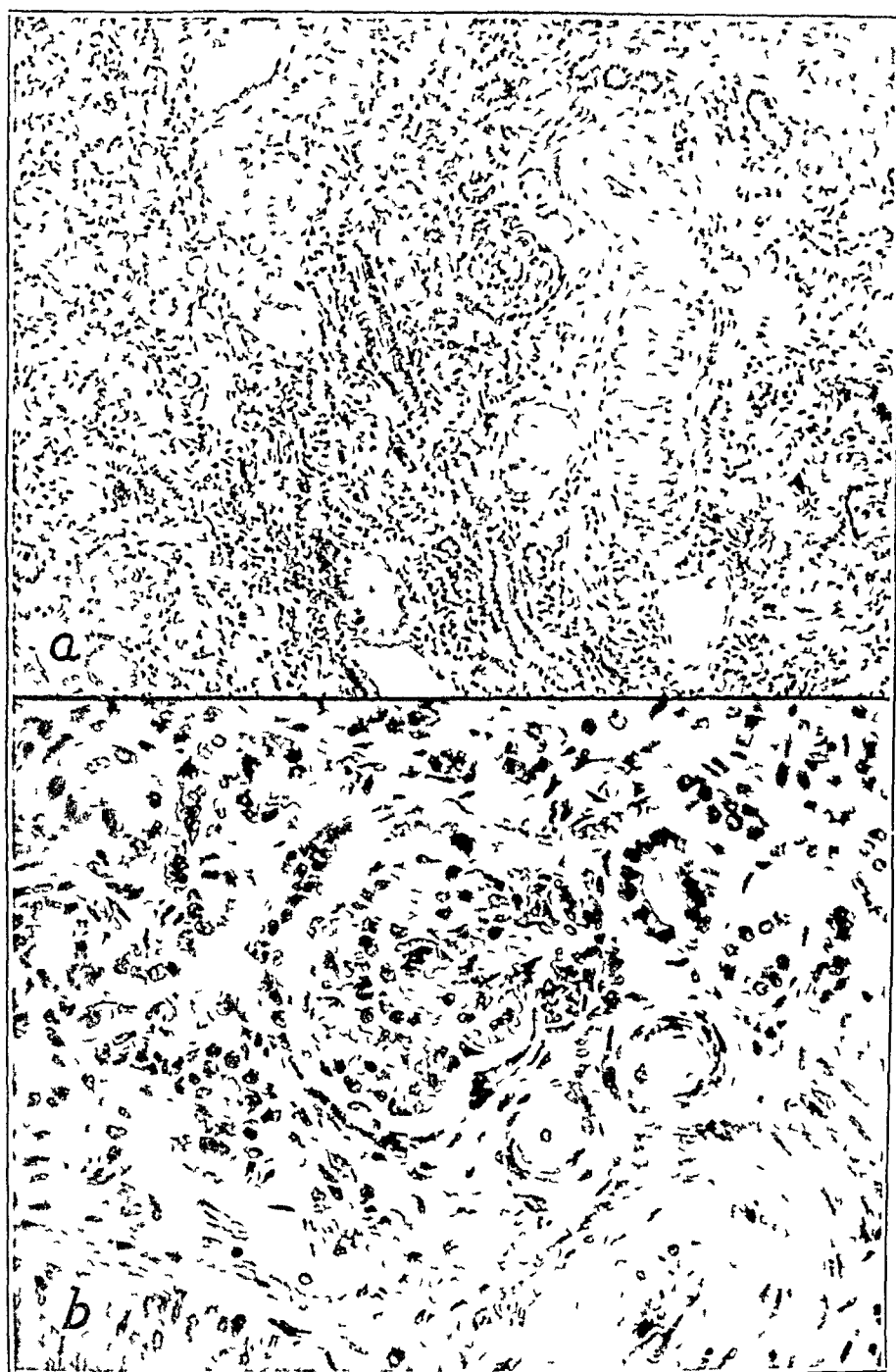


Fig 9 (case 7) —Sections of kidney (hematoxylin and eosin, *a*,  $\times 100$ , *b*,  $\times 320$ ) Pronounced arteriosclerosis and arteriolosclerosis, atrophy and dilatation of tubules and hyalinization of some glomeruli, whereas others appear only slightly injured. There is an increase in interstitial connective tissue.

results indicate that the kidneys of this patient were able to excrete potassium in the urine at a concentration six times that of the blood serum. However, this patient died thirteen days later, and chronic histopathologic changes in the kidney

administered 5 to 10 Gm of potassium chloride daily to their patient for eight days. During this period they demonstrated that considerable retention of potassium occurred. No estimations of the concentration of potassium in the serum of this patient or in that of Blumenfeldt's patient were recorded by the investigators in question. Therefore, the question as to whether or not such a degree of retention

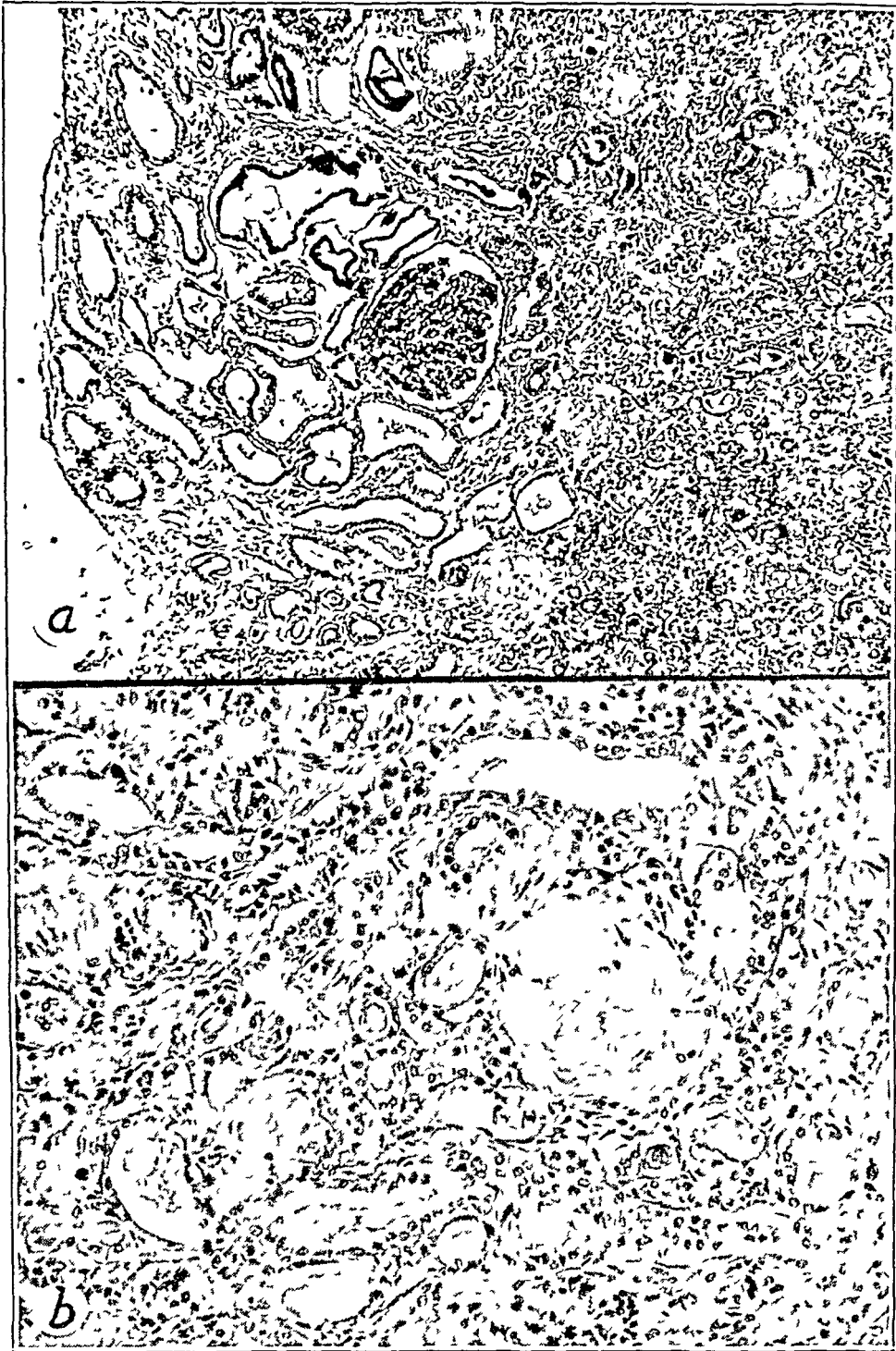


Fig 10 (case 19) —Sections of kidney (hematoxylin and eosin, *a*,  $\times 50$ , *b*,  $\times 150$ ) The patient died at home thirty-two days after dismissal from the hospital. No normal glomeruli are seen, most of them have been transformed into hyalinized masses of connective tissue. Some of the glomeruli have undergone necrosis, others reveal cellular proliferation. Many of the tubules are dilated and filled with debris, many are atrophied or undergoing necrosis. The arteries and arterioles are greatly thickened, some of them to the point of occlusion.

of potassium could lead to a distinct sustained increase of potassium in the serum was left unanswered.

concentration of serum potassium from a previous high level. Clearance of potassium and urea was determined at this time, and it will be noted that the clearance of both was reduced when compared with the clearance obtained during a control period three days before. This result might have been due to a reduction in the volume of urine, but it does suggest the possibility that the ingestion of 5 Gm of potassium bicarbonate had produced a temporary toxic effect on the kidneys of this patient.

Our results, therefore, in study of the clearances of potassium in severe chronic renal insufficiency compare closely with those of Winkler, Hoff and Smith.<sup>29</sup> These observers pointed out that the presence of a normal fasting clearance of potassium in a patient who has severe chronic nephritis suggests that kidneys so affected can excrete the basal daily amount of potassium resulting from tissue catabolism. However, when an extra amount of potassium must of necessity be excreted, these diseased kidneys excrete it more slowly than normal ones, and if this extra load continues there will be a slow accumulation of potassium within the body, so that

TABLE 7—*Clearance of Potassium and Urea in Severe Chronic Renal Insufficiency*

Case	Age, Yr	Sex	Body Surface Square Meters	Experimental Period, Min *	Urine			Whole Blood and Serum †		Whole Blood and Serum Clearance ‡			
					Minute Volume (V), Cc	Potassium (U), Gm per 100 Cc	Urea (U), Gm per 100 Cc	Potassium (S), Mm per 100 Cc	Urea (S), Mm per 100 Cc	Potassium		Urea	
										U × V	1.73	U × V	1.73
										S × BS ‡		B × BS ‡	
										Cc per Min		Cc per Min	
8	27	F	1.61§	60	1.05	0.129	0.713	17.8	291	8		3	
10	64	F	1.58	60	1.6	0.082	0.503	26.7	146	5		6	
				60	2.1	0.080	0.451	27.3	141	7		8	
				60	2.1	0.080	0.451	27.3	141	7		8	
16	31	F	1.54	68	1.97	0.064	0.409	21.4	170	6		5	
19	31	M	2.05	71	2.18	0.023	0.766	17.8	376	2		1	
20	48	F	1.69	60	3.1	0.080	0.502	21.4	201	13		9	
21	33	F	1.52	60	3.5	0.041	0.315	24.6	180	7		7	
22	20	M	1.66	60	1.6	0.094	0.725	21.4	348	7		3	
27	16	F	1.59	60	2.5	0.152	0.702	22.9	124	13		15	
				65§	0.95	0.247	0.725	17.3	118	7		6	

\* Urine collected by catheter at beginning and end of period in the morning before breakfast.

† Blood obtained at midperiod of experiment. Estimation of urea done on oxalated whole blood.

‡ Corrected for body surface of 1.73 square meters. BS means body surface.

§ Approximate.

|| Two experiments in case 10 and case 27, seven and three days apart, respectively.

¶ Patient took 5.0 Gm of potassium bicarbonate before the experiment.

actual retention will take place. The results of Winkler, Hoff and Smith,<sup>29</sup> who gave extra potassium to several patients with nephritis, are in harmony with this viewpoint. Previous support for the occurrence of such a series of events was given in 1913 by Blumenfeldt,<sup>30</sup> who found that potassium was being distinctly retained in a patient who had cardiac edema and chronic diffuse nephritis. However, in 1935 MacKay and Butler carried out a detailed metabolic study of a patient who had terminal chronic glomerulonephritis, and in whom edema was limited to the region of the ankles.<sup>31</sup> In addition to a known diet, these investigators

29 Winkler, A. W., Hoff, H. E., and Smith, P. K. The Toxicity of Orally Administered Potassium Salts in Renal Insufficiency, *J. Clin. Investigation* **20** 119-126 (March) 1941.

30 Blumenfeldt, E. Beiträge zur Kalausscheidung unter normalen und pathologischen Verhältnissen, *Ztschr. f. exper. Path. u. Therap.* **12** 523-528 (Feb. 22) 1913.

31 (a) MacKay, E. M., and Butler, A. M. Studies of Sodium and Potassium Metabolism. The Effect of Potassium on the Sodium and Water Balances in Normal Subjects and Patients with Bright's Disease, *J. Clin. Investigation* **14** 923-939 (Nov.) 1935. (b) Van Slyke, D. D., Stillman, E., Moller, E., Ehrlich, W., McIntosh, J. F., Leiter, L., MacKay, E. M., Hannon, R. R., Moore, N. S., and Johnston, C. Observations on the Courses of Different Types of Bright's Disease, and on the Resultant Changes in Renal Anatomy, *Medicine* **9** 257-386 (Sept.) 1930.

ingested, the mortality rate among these rats reached 50 per cent. Estimations of the concentration of potassium in the serum of the rats which had been fed potassium were not made by these investigators, but it naturally may be presumed that it was elevated.

Experiments in the laboratory reveal that bilateral nephrectomy, bilateral ligation of the ureters, bilateral exposure to roentgen rays and acute nephritis produced by uranium and mercury bichloride lead to an abnormal increase in serum potassium, or, in other words, to retention of potassium in the blood serum. Similar reactions are to be expected in acute experimental congestion of the kidneys. Thus, there is ample experimental evidence that potassium may be abnormally retained in the blood stream by acutely decompensated kidneys. This fact leads to consideration of the toxicity of potassium salts when given to animals which have so-called uranium nephritis. Smillie<sup>34</sup> in 1915 reported results of such experiments in rabbits and noted that sudden death frequently occurred. He attributed these fatalities to the rapid retention of potassium in the blood and its subsequent toxic action on the heart, but he did not actually estimate the concentration of potassium in the blood. In this connection the results of experiments by Bergman and Drury<sup>35</sup> in bilateral nephrectomized rats appear to be important. They found that the ingestion of ash containing a considerable amount of potassium decidedly reduced the survival period when it was compared with the survival period of control animals. Hoff and his co-workers also showed that when a potassium salt was given to a dog which had anuria due to either bilateral nephrectomy or ligation of the ureters, the survival period was decreased. Hoff and his associates further revealed by means of electrocardiographic studies that death among these anuric animals was due to a great increase in the concentration of potassium in the blood plasma, which finally caused cardiac failure. To date the evidence of retention of potassium in cases of severe acute clinical renal damage is meager. In Darrow's case in which a child had acute glomerulonephritis (reported by Hoff and associates) the value for potassium in the serum was high. Beall, Bywaters, Belsey and Miles<sup>36</sup> also found that the value for potassium in the serum was very high in a case, complicated by renal failure, after injury to a leg had been inflicted by crushing. Both these observations are of interest in this connection. Therefore, cases of acute renal insufficiency, including cases of acute glomerulonephritis and the toxic nephritides, such as acute intoxication with mercury bichloride or with bismuth, offer a unique opportunity for further study of the potassium problem in relation to renal disease. Future investigation in cases in which the condition is acute should include frequent estimations of the concentration of potassium in the serum and simultaneous electrocardiographic tracings. Our observations in case 15 during the terminal phase of chronic renal disease indicate that the electrocardiogram may reveal alterations very suggestive of intoxication with potassium.

In contrast to the probable toxic effects of a potassium salt in patients who have severe renal failure is the well recognized clinical experience of many observers that large doses of such a salt may be ingested by patients suffering from chronic nephritis with edema without noticeable harmful results, this was the experience

34 Smillie, W. G. Potassium Poisoning in Nephritis, *Arch. Int. Med.* **16** 330-339 (Aug.) 1915.

35 Bergman, H. C., and Drury, D. R. A Study of Acute Renal Insufficiency, *J. Clin. Investigation* **18** 777-781 (Nov.) 1939.

36 Beall, D., Bywaters, E. G. L., Belsey, R. H. R., and Miles, J. A. R. A Case of Crush Injury with Renal Failure, *Brit. M. J.* **1** 432-434 (March 22) 1941.



## COMMENT

It seems clear that potassium metabolism may be disturbed in the presence of renal disease. However, at present this disturbance of potassium metabolism cannot be as readily demonstrated as can that of some other substances actively excreted by the kidney. The observations of previous investigators and the results of the present study agree in revealing that a single estimation of the concentration of serum potassium in the presence of severe renal insufficiency may give a result that is normal, increased or decreased. But when several estimations are made of the serum of the same patient during the course of renal insufficiency, as was done on the serum of many of our patients, it is evident that at some time the content of potassium in the serum may become abnormally high. In such an instance, again, any factor that decreases the intake or disturbs the output of potassium, such as anorexia, vomiting<sup>32</sup> or diarrhea, may lower its concentration in the blood serum. Other factors that perhaps prevent a steadily increasing retention of potassium in the blood by severely damaged kidneys are the relatively good fasting urinary clearance of potassium and the development of polyuria. The increased output of water in the presence of chronic renal disease may permit the excretion of potassium at a low rate, but in total amounts which are nevertheless sufficient in twenty-four hours to keep the concentration in the serum from increasing to abnormal levels.

A review of the observations of others on renal disease and the results in this series of cases indicate that high values for potassium in the serum are more usually obtained when rapid renal failure occurs. The closer renal insufficiency is to total loss of renal function, the more likely it seems that the excretion of potassium is disturbed. Such rapid renal failure may take place in acute, subacute and congestive renal disease, it also may occur in chronic nephritis, especially during an acute exacerbation or in the terminal phase. Indeed, an abnormally high value for potassium in the serum may possibly indicate that an acute phase is present during the course of chronic renal disease.

Previous observers have stressed the presence of marked oliguria or anuria when the concentration of potassium in the serum increases. We have had a similar experience but have also observed in the serum of several patients an increase in serum potassium to between 30 and 40 mg per hundred cubic centimeters at the same time that a considerable volume of urine was being excreted. This observation supports the viewpoint that in the presence of severe renal insufficiency, when the output of water is ample, there may be at a given time a greater disturbance in the excretion of a single substance (in this instance potassium) than in the excretion of others.

The occurrence of a high value for potassium in the serum of human beings who have congestion of the kidneys and oliguria seems to be of serious import and indicative of the renal retention of potassium. In this connection the results of Addis and Lew<sup>33</sup> in experimental studies seem to be significant. They have shown that congestion of the kidneys of the rat produced by ligation of the inferior vena cava above the renal veins gives rise to oliguria and severe acute renal insufficiency. With the rapid establishment of collateral venous circulation, however, the renal congestion soon disappears, and within seven days normal renal function is restored. If before and during the acute congestive phase a potassium salt was

32 Falconer, M. A., Osterberg, A. E., and Barger, J. A. Intestinal Obstruction in Man. Alterations in the Serum Bases and Their Significance, *Arch Surg* **38** 869-885 (May) 1939.

33 Addis, T., and Lew, W. Diet and Death in Acute Uremia, *J Clin Investigation* **18** 773-775 (Nov.) 1939.

volume of distribution of potassium throughout the body had become less because of dehydration?<sup>41</sup>

Since ionic equilibrium is known to be influenced by certain hormones of the glands of internal secretion, and particularly by compounds elaborated by the adenal cortex, it seemed important to evaluate any possible relationship that might obtain between the ionic pattern of the serum in renal insufficiency and alterations in the adenal bodies. In the presence of severe chronic renal insufficiency the content of potassium in the serum may be abnormally elevated and that of sodium reduced, a pattern similar to that seen in cases of adrenal insufficiency. We therefore examined carefully the adrenal bodies of 13 persons who had come to necropsy, and, as stated earlier in this paper, we were unable to find any gross or unmistakable histologic evidence of adrenal abnormality. Of course, negative results of histologic study do not rule out a possible functional alteration in these bodies. In certain cases in which the condition belongs to the so-called Cushing syndrome, changes occur in electrolytic metabolism, including an abnormally low concentration of potassium in the serum. This has been noted by McQuarrie, Johnson and Ziegler<sup>42</sup> and by Willson, Power and Kepler<sup>43</sup>. In none of the cases in this series did the clinical observations suggest such a syndrome, and the characteristic lesions in the adrenal cortex sometimes found in such cases were absent. In the 13 cases in which pathologic studies were carried out, however, changes in the pituitary body could not be excluded because this body was not examined by the pathologist. The evidence at hand from this study therefore does not support the viewpoint that the disturbances in potassium metabolism encountered were due to endocrine dysfunction.

The actual excretion and retention of different inorganic ions by the kidney is of great physiologic interest. Study of the individual excretion of these ions has been greatly stimulated by the development of accurate microchemical methods. For example, it is known that inorganic sulfates are readily excreted, but in a manner different from that in which chlorides are excreted. The chlorides, together with sodium, may be noticeably retained by the kidney, especially when the intake of these ions is small. The renal clearance of potassium in the starving normal person is remarkably small, being approximately 10 to 12 per cent of that of inulin. Since inulin is considered to be excreted by the kidney entirely by a process of glomerular filtration and since the potassium ion is also thought to be filtered readily by the glomeruli, the small clearance of potassium suggests that a relatively large percentage of that filtered by the glomeruli is reabsorbed by the tubules. Such a cycle of filtration and reabsorption within the kidney is analogous to the excretion of potassium into the stomach and its reabsorption into the blood from the large bowel<sup>44</sup>. We have obtained, however, some interesting results among normal persons in whom dehydration occurred after the ingestion of large doses of a potassium salt. The clearance of inulin decreased and that of potassium increased,

41 Winkler, A. W., and Smith, P. K. The Apparent Volume of Distribution of Potassium Injected Intravenously, *J Biol Chem* **124** 589-598 (Aug.) 1938. Winkler, A. W., Hoff, H. E., and Smith, P. K. Toxicity of Potassium in Adrenalectomized Dogs, *Am J Physiol* **133** 494-495 (June) 1941.

42 McQuarrie, I., Johnson, R. M., and Ziegler, M. R. Plasma Electrolyte Disturbance in Patient with Hypercorticoadrenal Syndrome Contrasted with That Found in Addison's Disease, *Endocrinology* **21** 762-772 (Nov.) 1937.

43 Willson, D. M., Power, M. H., and Kepler, E. J. Alkalosis and Low Plasma Potassium in a Case of Cushing's Syndrome. A Metabolic Study, *J Clin Investigation* **19** 701-707 (Sept.) 1940.

44 Fenn, W. O. The Role of Potassium in Physiological Processes, *Physiol Rev* **20**: 377-415 (July) 1940.

of Wilks and Taylor<sup>37</sup> in 1863 our experience in 1935<sup>21</sup> and in 2 cases of the present series and also that of Winkler, Hoft and Smith<sup>38</sup> during the past year (1941). The actual doses that have produced toxic effects on the kidney in 2 normal men under our care were very much larger than those prescribed in clinical medicine<sup>39</sup>. This also applies to experiments conducted on 3 normal men in whom dehydration as well as reduced renal function resulted from the ingestion of large doses of a potassium salt<sup>39c</sup>. There are, no doubt, patients who have chronic nephritis with moderate retention of urea and an increased concentration of potassium in the serum, similar to that in our cases 24, 26 and 27, to whom it may be dangerous to administer moderate doses of a potassium salt, but they are probably few. We had previously cautioned against the administration of potassium salts to patients who have nephritic edema and a concentration of urea in the blood of more than 100 mg per hundred cubic centimeters. That some of these patients may have a lessened tolerance for potassium and even an increased value for potassium in the serum lends support to such a precaution. It seems clear, therefore, that a persistently high value for potassium in the serum is of serious prognostic import in any case of renal disease. Its presence in nephritic patients during an acute phase, in patients who have subacute or chronic processes associated with edema or in patients suffering from cardiac disease with severe passive congestion should forbid any sort of diuretic therapy which includes the administration of a potassium salt, an acid-producing salt or an organic mercury compound. In such cases the use of any of these substances may lead to serious complications.

In addition to renal insufficiency, alterations in metabolism may cause an abnormal increase in potassium in the serum, for example, when increased catabolism occurs, as in fasting or when fever is present. In these conditions, the breakdown of tissue protein is accelerated, and an increased amount of potassium is thus liberated from tissue cells and passes into the circulation to cause an increase in the concentration of potassium. A single report by Gamble, Ross and Tisdall<sup>40</sup> concerning a fasting child discloses a high normal value for serum potassium, which decreased after the child had resumed the ingestion of a carbohydrate diet. In the presence of fever a series of events similar to those in fasting probably occurs, and such an explanation seems to be the most satisfactory one for our observations in case 11 of the present series. Dehydration also may play a role in causing an increase in potassium in the serum. In 1935 Keith and Binger<sup>24</sup> reported some interesting results of experiments conducted on 3 normal persons and a patient who had chronic polyserositis, in which dehydration apparently developed. To each of these persons was given a diet low in both mineral salts and water and also extra potassium, 50 to 80 mg per kilogram of body weight, daily for several days. In the serum of each person an increase occurred in the concentration of potassium to 33 to 40 mg per hundred cubic centimeters without obvious retention of potassium by the kidneys. Is it possible that in these persons the

37 Wilks, and Taylor, A. S. Case in Which Large Quantity of Nitrate of Potash Was Taken Medicinally. Elimination of the Salt by the Urine, *Guy's Hosp Rep* **9** 173-179, 1863.

38 Footnote deleted on proof.

39 (a) Keith, N. M., Osterberg, A. E., and Burchell, H. B. Some Effects of Potassium Salts in Man, *J Pharmacol & Exper Therap* **72** 22-23 (May) 1941, Some Effects of Potassium Salts in Man, *Ann Int Med* **16** 879-892 (May) 1942. (b) Keith, N. M., and Osterberg, A. E. The Excretion of Potassium by the Kidney, *Am J Physiol* **129** 395-396 (May) 1940. (c) Keith, N. M., Osterberg, A. E., and King, H. E. The Excretion of Potassium by the Normal and Diseased Kidney, *Tr A Am Physicians* **55** 219-222, 1940.

40 Gamble, J. L., Ross, G. S., and Tisdall, F. F. The Metabolism of Fixed Base During Fasting, *J Biol Chem* **57** 633-695 (Oct) 1923.

## METHODS OF CHEMICAL ANALYSIS EMPLOYED IN THE PRESENT STUDY

## WHOLE BLOOD

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*Urea*—Van Slyke, D D, and Cullen, G E A Permanent Preparation of Urease, and Its Use in the Determination of Urea, *J Biol Chem* **19** 211-228, 1914

*Creatinine*—Folin, O Laboratory Manual of Biologic Chemistry, ed 3, New York, D Appleton and Company, 1922, pp 149, 245 and 247

## PLASMA

*Chloride*—Osterberg, A E, and Schmidt, E V The Estimation of Plasma Chlorides, *J Lab & Clin Med* **13** 172-175 (Nov) 1927

*Carbon Dioxide-Combining Power*—Van Slyke, D D, and Cullen, G E Studies of Acidosis I Bicarbonate Concentration of the Blood Plasma, Its Significance and Its Determination as a Measure of Acidosis, *J Biol Chem* **30** 289-346, 1917

*Cholesterol*—Bloor, W R The Determination of Cholesterol in the Blood, *J Biol Chem* **24** 227-231, 1916

## SERUM

*Total Proteins*—Macro-Kjeldahl technic of estimation of total nitrogen and total protein, calculated after subtracting nonprotein nitrogen as estimated by the micro-Kjeldahl method

*Albumin and Globulin Fractions*—Howe, P E The Determination of Proteins in Blood A Micro Method, *J Biol Chem* **49** 109-113 (Nov) 1921 Kingsley, G R A Rapid Method for Separation of Serum Albumin and Globulin, *ibid* **133** 731-735 (May) 1940

*Potassium*—Kramer, B, and Tisdall, F F A Clinical Method for the Quantitative Determination of Potassium in Small amounts of Serum, *J Biol Chem* **46** 339-349 (April) 1921

This method in our hands has checked with gravimetric procedures The precipitation by sodium cobaltinitrite was allowed to proceed for forty-five minutes at ice box temperature in order to obtain a good, granular precipitate If this and other steps are rigorously adhered to, the method is satisfactory Potassium in urine was estimated after ashing by this method

*Sodium*—Kramer, B, and Gittleman, I An Iodometric Method for the Determination of Sodium in Small Amounts of Serum, *J Biol Chem* **62** 353-360 (Dec) 1924

*Calcium*—Clark, E P, and Collip, J B A Study of the Tisdall Method for the Determination of Blood Serum Calcium with a Suggested Modification, *J Biol Chem* **63** 461-464 (March) 1925

*Phosphorus*—Kuttner, T, and Lichtenstein, L Micro Colorimetric Studies II Estimation of Phosphorus, Molybdic Acid-Stannous Chloride Reagent, *J Biol Chem* **86** 671-676 (April) 1930

*Sulfate*—Power, M H, and Wakefield, E G A Volumetric Benzidine Method for the Determination of Inorganic and Ethereal Sulfate in Serum, *J Biol Chem* **123** 665-678 (May) 1938

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*Total Nitrogen*—Kjeldahl, J Neue Methode zur bestimmung des Stickstoffs in organischen Korpern, *Ztschr f anal Chem* **22** 366-382, 1883

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*Potassium*—Same method as for estimation in serum except that urine is ashed before precipitation

*Total Proteins*—Macro-Kjeldahl method for estimation of total nitrogen Estimation of non-protein nitrogen by macro-Kjeldahl method after precipitating the protein with Folin's tungstic acid reagent method Total proteins calculated after subtracting the nonprotein nitrogen from the total nitrogen and multiplying by 6.25

so that the potassium inulin ratio was greater than unity, suggesting actual tubular secretion of potassium. McCance and Widdowson<sup>45</sup> reported a similar result in a patient who had alkalosis. The normal kidney therefore appears to play a dual role in the metabolism of potassium in that it possesses ready mechanisms for both the excretion of potassium into the urine and the reabsorption and ultimate retention of it in the blood stream. The abnormal retention of urea and potassium in the blood, the excessive excretion of sodium in the urine in the presence of adrenaal insufficiency and the remarkable restoration to normal of values for these substances when an extract of the adrenal cortex is administered naturally suggest that the adrenaal cortical hormone which has to do with the metabolism of water and inorganic ions may be an important regulating factor in the normal renal metabolism of potassium. Further investigation of this possible relationship between renal and adrenaal functions with regard to potassium might throw light on the intracellular function of potassium in the renal tubules.

The normal kidney excretes potassium in an oscillating manner. The low clearance of potassium in fasting states suggests regulation to prevent excessive loss. On the other hand, the rapid increase in its clearance after a considerable amount of it is ingested indicates regulation to prevent excessive retention. This regulation of the renal excretion of potassium evidently plays an important role in control of the level of its concentration in the blood serum. On the basis of results of studies, such as the present one, on renal disease we have learned that the concentration of potassium in the serum is held within a rather narrow range. The highest concentration encountered in our series of patients was 41 mg per hundred cubic centimeters, or approximately twice the normal concentration, and was found at a time when marked chronic renal insufficiency was present. The consistent ability of seriously damaged kidneys to keep up a normal fasting clearance of potassium unquestionably is one factor in the prevention of too great an increase in potassium in the serum. We know, however, that there are also extrarenal factors, such as dehydration, excessive tissue catabolism and the volume of distribution of potassium throughout body fluids and tissue cells, which may have a similar effect. One obvious reason for both these regulatory mechanisms, renal and extrarenal, is prevention of the concentration of potassium in the serum from rising too high, for there is considerable evidence that a concentration of between 40 to 60 mg per hundred cubic centimeters may be markedly toxic to the cells of many different tissues (up to the present time this can best be demonstrated in those of the heart).

#### SUMMARY

Disturbances of potassium excretion are sometimes difficult to demonstrate in the presence of renal disease. They occur more frequently than has been suspected. When severe renal dysfunction develops in acute or subacute nephritis, in the terminal stage of chronic nephritis or in marked congestion of the kidney, potassium is more slowly excreted into the urine and the concentration of it in the blood serum may increase to twice the normal value. Several factors, both renal and prerenal, appear to hinder increase in the concentration of potassium in the serum, and this curb on such an increase seems to be more effective in man than in the experimental animal. When a sustained increase in serum potassium does occur in renal disease, however, it is of serious prognostic import and should forbid the therapeutic use of a potassium salt.

<sup>45</sup> McCance, R. A., and Widdowson, E. M. Alkalosis with Disordered Kidney Functions. Observations on a Case, *Lancet* 2: 247-249 (July 31) 1937.

## THE NORMAL ADRENAL GLAND

In only 3 cases included in the series could the adrenal glands be classified as normal. These were cases of sudden death occurring in previously healthy persons. The combined adrenal weights were 10.05, 9.60 and 8.79 Gm, respectively. These values conform with those of Kiyokawa,<sup>6</sup> Materna<sup>7</sup> and Kraus.<sup>8</sup> Other authors, on the other hand, including Scheel,<sup>9</sup> Schif, <sup>10</sup> Jaffe and Sternberg<sup>11</sup> and Dietrich,<sup>12</sup> have reported weights of 11.2, 11.4, 13.5 and 10 to 16 Gm, respectively. Materna's figures were based on findings in 25 cases of sudden death occurring in young previously healthy males. Dietrich and Siegmund<sup>13</sup> considered Materna's values to be correct and concluded that the higher values of other authors were associated with prolonged disease. This point of view is substantiated in the present series, the weight of the vast majority of the glands averaging between 11 and 13.5 Gm.

The classic histologic description of the adrenal cortex divides it into three layers: zona glomerulosa, zona fasciculata and zona reticularis. Sudan imparts an orange color to all lipoids, including cholesterol. The normal cortex exhibits a typical arrangement of sudanophilic material (fig. 4). The greatest concentration of lipoids is in the outer half of the zona fasciculata, while somewhat less is in the zona glomerulosa, and even less is present in the inner half of the zona fasciculata and the zona reticularis. This lipoid pattern was established by Mulon<sup>14</sup> and Landau.<sup>15</sup> Landau and later Zwemer<sup>16</sup> elaborated Gottschau's original dynamic concept that the cells composing the adrenal cortex grow by mitotic division in the outermost layer (glomerulosa) and, during their life cycle, migrate through the zona fasciculata, eventually to die in the zona reticularis. On the basis of a histochemical technique employing phenylhydrazine and digitonin to demonstrate cortical ketosteroids and cholesterol, respectively, Bennett<sup>17</sup> preferred to call the zona glomerulosa the presecretory layer and subdivided the zona fasciculata into the secreting and the postsecretory layer, terming the zona reticularis the senescent layer. The secreting outer half of the zona fasciculata corresponds to the area of greatest lipoid content. When these histochemical procedures are employed with selected human adrenal glands exhibiting various types of lipoid patterns, it is seen that the distribution of the ketosteroids and cholesterol corresponds closely to the intensity of the

6 Kiyokawa, W. Die Nebennieren bei Tuberkulose, Frankfurt Ztschr. f. Path. **29** 287, 1923.

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9 Scheel, O. Ueber Nebennieren, Virchows Arch. f. path. Anat. **192** 494, 1918.

10 Schif, D. Die quantitativen Beziehungen der Nebennieren zum übrigen Körper, Ztschr. f. Konstitutionslehre **8** 507, 1923.

11 Jaffe and Sternberg, cited by Dietrich and Siegmund<sup>13</sup>.

12 Dietrich, A., in Henke, F., and Lubarsch, O. Drüsen mit innerer Sekretion, in Handbuch der speziellen pathologischen Anatomie und Histologie, Berlin, Julius Springer, 1926, vol. 8, p. 964.

13 Dietrich, A., and Siegmund, H., in Henke, F., and Lubarsch, O. Drüsen mit innerer Sekretion, in Handbuch der speziellen pathologischen Anatomie und Histologie, Berlin, Julius Springer, 1926, vol. 8.

14 Mulon, P. Note sur la capsule surrénale du mouton, considerations histo-physiologiques, Bibliog. anat. **22** 30, 1912.

15 Landau, M. Die Nebennierenrinde, Jena, Gustav Fischer, 1915.

16 Zwemer, R. L. A Study of Adrenal Cortex Morphology, Am. J. Path. **12** 107, 1936.

17 Bennett, H. S. Life History and Secretion of Cell of Adrenal Cortex of Cat, Am. J. Anat. **67** 151, 1940.

# ADRENAL CORTEX IN SYSTEMIC DISEASE

## A MORPHOLOGIC STUDY

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With the extraction of an active substance by Swingle and Pfiffner<sup>1</sup> and Hartman and Brownell<sup>2</sup> in 1930 and the more recent isolation of potent crystalline compounds by Reichstein<sup>3</sup> and Kendall and his associates,<sup>4</sup> great advances have been made in the knowledge of the physiology of the cortex of the adrenal gland. The effects of its hormones are reasonably well known today. The influence of systemic disease on the morphologic appearance of the gland is, however, not widely recognized. The latter, described by many, could not have been appreciated without the benefit of the more recent advances in the knowledge of the physiology of the gland. An attempt will be made in this paper to establish correlations between changes in the morphologic aspects of the cortex and various systemic diseases.

## MATERIAL

Adrenal glands were obtained from 110 routine autopsies performed at the New Haven Hospital (one to six hours after death). No glands from persons with Addison's disease or primary neoplasm of the adrenal gland are contained in the series. The organs were dissected out of their beds with a small amount of surrounding tissue, thereby avoiding trauma to the delicate glands. They were immediately placed unsectioned in 4 per cent solution of formaldehyde, where they were allowed to remain for two days. On removal, they were carefully freed of all attached tissues, gently dried with paper toweling, and weighed on a torsion balance to the nearest hundredth of a gram. (A review of the weights of adrenal glands recorded in autopsy protocols over a twenty year period in the New Haven Hospital revealed wide discrepancies. It was deemed necessary, therefore, to employ this somewhat tedious procedure to determine the significance of the weights.) Serial longitudinal sections were made of each gland, a single representative block being taken from the widest portion unless gross examination warranted taking of others. Frozen sections, cut at 10 to 20 microns, were stained with sudan III (Herzheimer)<sup>5</sup> and counterstained with Harris' hematoxylin. The remainder of this block was embedded in paraffin, and sections were cut at 4 to 8 microns and stained with hematoxylin and eosin.

Since it is the purpose of this paper to correlate morphologic changes of the adrenal gland with systemic diseases, a careful review was made of the clinical history and general autopsy findings in each case. Special attention was paid to metabolic disturbances known to be intimately related to disorders of adrenal function. In addition to the usual pathologic conditions seen at the autopsy table, including hypertensive cardiovascular renal disease, generalized arteriosclerosis (nonhypertensive), infectious disease, cancer and diabetes, several examples of erythroblastosis foetalis, as well as cases with clinical manifestations of adrenal insufficiency, are contained in the series.

This investigation was aided by a grant from the Commonwealth Fund.

From the Laboratory of Pathology, Yale University School of Medicine.

1 Swingle, W. W., and Pfiffner, J. J. An Aqueous Extract of the Suprarenal Cortex Which Maintains the Life of Bilaterally Adrenalectomized Cats, *Science* **71** 321, 1930.

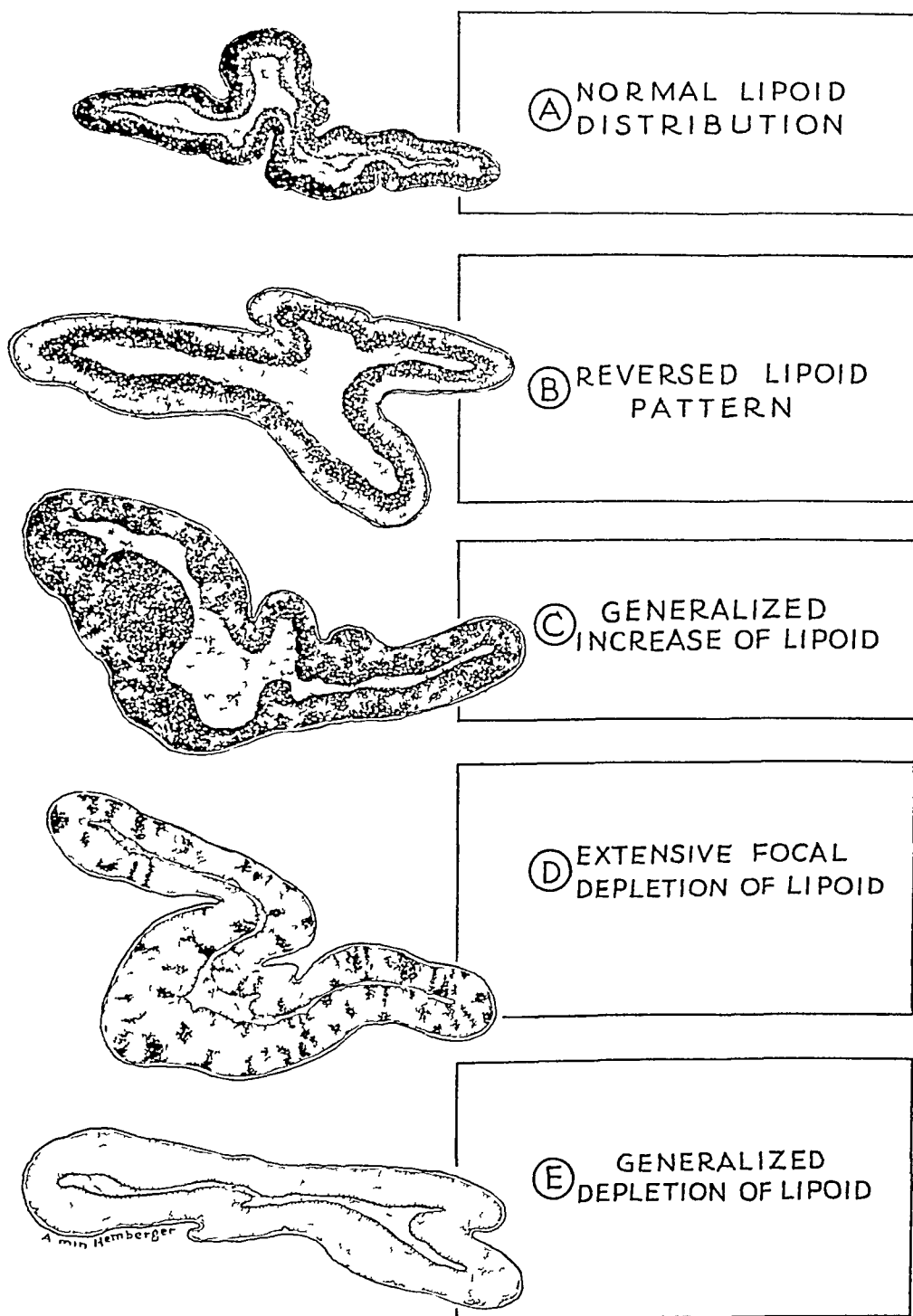
2 Hartman, F. A., and Brownell, K. A. The Hormone of the Adrenal Cortex, *Science* **72** 76, 1930.

3 Reichstein, R. Ueber Cortin, das Hormon der Nebennierenrinde, *Helvet. chim. acta* **19** 29, 1936.

4 Kendall, E. C., Mason, H. L., Hoehn, W. M., and McKenzie, B. F. Studies in the Chemistry of the Suprarenal Cortex, *Proc. Staff Meet., Mayo Clin.* **12** 136, 1937.

5 Schmorl, G. Die pathologisch-histologischen Untersuchungsmethoden, Leipzig, F. C. W. Vogel, 1934.

of these cells was homogeneously eosinophilic, lacking the usual foamy appearance. The interstitium between the cords of the zona fasciculata was the site of edema and hyperemia. Focal hemorrhages and polymorphonuclear infiltrations were seen occasionally. No bacterial emboli were noted.



A diagrammatic representation of the distribution of lipid in the cortex of the adrenal gland

All of the adrenal glands of the 28 adults with inflammatory diseases exhibited depletion of cortical lipid or alteration in its distribution. In 21 cases these changes were associated with marked enlargement. In 5 of the remainder the glands were moderately enlarged and in 2 they were of normal size. Adenomas were found only twice.



sudanophilic material Therefore, the phenylhydrazine and digitonin technics were not employed routinely with the human material, as it was believed that the all-inclusive sudan stain served the purpose adequately

#### INFECTIOUS DISEASE

The adrenal glands from 28 adults with active inflammatory diseases are included in the series Marked enlargement of the glands was commonly seen Their average combined weight was 15.1 Gm, the values ranging from 10.40 to 23.55 Gm as can be seen from table 1, almost half the glands weighed more than 16.0 Gm

Of the 28 adults, 13 had acute inflammatory diseases, including 2 with gangrenous appendicitis and peritonitis, 2 with necrotizing pneumonia, 7 with septicemia resulting from various portals of entry, 1 with interstitial myocarditis, and 1 with acute pemphigus The average combined adrenal weight in this group was 16.6 Gm, the weight being below 15.47 Gm in only 3 instances

Fifteen of the 28 adults had chronic inflammatory diseases, associated with acute exacerbations in some The average combined adrenal weight was 13.4 Gm, in contrast with 16.6 Gm the average for the group with acute inflammatory disease

TABLE 1—*Weight of Combined Adrenal Glands of Twenty-Eight Adults with Active Inflammatory Disease*

Combined Adrenal Weight, Gm	Incidence
10.40-11.95	10
13.24-13.82	3
15.47-16.00	3
16.17-18.81	9
20.41-23.55	3

Most of the adrenal glands from the group with active inflammatory diseases showed moderate to marked enlargement The depletion of the cortical lipid was apparent on gross examination The usual yellow-orange color of the cortex had been transformed into pale gray Focal patches of orange material were often seen dotting the cut surface, indicating the remnants of what was formerly a solid orange band Microscopic examination disclosed varying degrees of lipid depletion of the cortex associated with atypical distribution of this material, it was now in the inner instead of the outer part of the zona fasciculata (fig, B) In extreme cases no sudanophilic material remained in the cortex (fig, E) Other glands, showing less of this change, exhibited focal areas of lipid-containing cells interspersed with fat-free areas (fig, D) The usual solid sudanophilic band of the cortex of the least involved glands was punctuated by circumscribed foci of lipid depletion The latter resembled foci of demyelination as seen in the Weigert stain These variations in cortical lipid content and distribution were best appreciated with the lower power lens or the naked eye In some instances the sudanophilic material appeared as more finely particulate than usual Central nonstaining vacuolation of some of the larger droplets of sudanophilic material was also evident Some of the cells in the zona fasciculata possessed honeycombed cytoplasm, which proved not to be sudanophilic Such cells were present in large numbers in some cases and were easily distinguished from the normal foamy lipid-containing cells In the hematoxylin eosin preparation, nests of small round cells were present in the glomerulosa layer These cells did not contain lipid The cords of cells composing the zona fasciculata were slender, and the cytoplasm

## DIABETES MELLITUS

It is impossible to evaluate any changes in the adrenal cortex in the cases of this group since 8 of the 9 patients had complicating hypertension or inflammatory disease. The changes noted were those seen in connection with the latter two conditions. In the sole uncomplicated case there was no alteration in adrenal weight or histologic picture.

## CIRRHOSIS

The 5 cases of cirrhosis of the liver included in this series were complicated by infectious processes, diabetes or severe long-standing anemia. Hence, the morphologic changes observed in the adrenal glands cannot be correlated with the underlying disease of the liver. All of the glands except a single pair were moderately enlarged and showed depletion of cortical lipid or a reversal of the lipid pattern. In the single uncomplicated case of biliary cirrhosis occurring in a 29 year old woman the adrenal glands were of normal weight and histologic appearance.

TABLE 2—Data on Children and Newborn Infants

Age	Sex	Diagnosis	Adrenal Glands	
			Weight, Gm	Histologic Change
15 mo	M	Pneumococcal meningitis	2.84	Lipoid depletion
6 mo	M	Retarded development (3.9 Kg)	9.77	Lipoid depletion
3 yr	M	Bacillary dysentery	4.22	Lipoid depletion
4 yr	F	Encephalomyelitis	4.60	Regular lipid pattern
Premature Newborn Infants				
6.7th mo	F		2.07	No lipid in zona glomerulosa
7th mo	F	Jaundice, aspiration	4.25	No lipid in zona glomerulosa, hemorrhage in zona fasciculata
Full Term Newborn Infants				
1 day	M	Diaphragmatic hernia	6.50	Minimal lipid in outer zona glomerulosa, sudanophil band comprising inner part of zona glomerulosa and outer part of zona fasciculata, fine sudanophilic material in inner part of zona fasciculata and zona reticularis
3 days	M	Aspiration	5.70	Similar to above
11 days	M	Pneumococcal meningitis	7.48	Lipoid depletion (marked), foci of necrosis

## CHILDREN AND NEWBORN INFANTS

The adrenal glands of only 2 premature infants, 3 full term newborn infants and 4 children are included in this series. Therefore, no conclusive observations can be made. The pertinent data are tabulated in table 2.

## ERYTHROBLASTOSIS FOETALIS

Because of the striking enlargement of the adrenal glands, 4 examples of erythroblastosis foetalis have been grouped separately. The accurate combined adrenal weight in 2 cases was 17.30 and 12.16 Gm, and in the other 2 (collected prior to the beginning of this study), approximately 15 Gm each. In view of these findings the determination of the water content of the enlarged glands seemed indicated. The dry weight of the adrenal glands weighing 17.30 Gm was 3.32 Gm, i. e. 80 per cent water content. This corresponds approximately to the 75 per cent water content found in normal weight adrenal glands of the newborn. From this it can be concluded that the increase in weight of the adrenal glands in erythroblastosis foetalis cannot be attributed to edema.

The adrenal glands in these 4 cases of erythroblastosis showed much the same microscopic picture. The lipid pattern resembled that seen in the adrenal glands

## HYPERTENSION

Twenty cases of hypertension associated with cardiac hypertrophy form the next group. In 13 of these nephrosclerosis was present. The cases were about evenly distributed between males and females, with the ages varying between 35 and 76 years. The average combined weight of the adrenal glands was 15.9 Gm, two thirds weighing more than 13.5 Gm. The abundant lipid seen in the widened cortex on gross examination was striking. In 5 cases the adrenal glands were marked by adenomatous hyperplasia. Histologically, the inner as well as the outer zona fasciculata contained abundant lipid. Only in 3 cases, which were complicated by inflammatory disease (phagedenic ulcers, necrotizing vascular disease and extensive myomalacia) were foci of lipid depletion noted in the outer part of the zona fasciculata. All of the others showed a generalized increase in cortical lipid (fig. C).

In the remaining 7 cases of the hypertensive group chronic glomerulonephritis or pyelonephritis was a feature. The patients were 5 females and 2 males, their ages ranging between 22 and 61 years. The average combined weight of the adrenal glands was 12.58 Gm, only one third of them exceeding 13.5 Gm. (It will be recalled that the adrenal glands of two thirds of the group with nephrosclerosis exceeded the weight of 13.5 Gm.) Excessive amounts of lipid were present in the cortex in 4 cases. Of the 3 remaining, 1, complicated by necrotizing vascular disease, showed foci of lipid depletion in the zona fasciculata. Similar changes without associated complicating disease were found in the second, and the normal cytoarchitecture and lipid distribution were present in the third. It may be emphasized that adenomatous hyperplasia was present in only 1 case.

## NEOPLASTIC DISEASE

Thirteen instances of neoplastic disease are included in the present study. In surveying the adrenal weights in this group it became apparent that in the cases in which cachexia was associated with neoplastic disease the adrenal glands were larger than those of the patients dying without significant loss of weight. The adrenal glands of 5 of the 6 patients of the cachectic group weighed between 11.93 and 17.85 Gm, averaging 14.30 Gm. These showed varying degrees of lipid depletion. One pair exhibited the normal lipid pattern. In contrast to the marked increase in adrenal weight and associated lipid depletion seen in the cachectic patients were the normal lipid pattern and the slight increase in adrenal weight found in the glands of patients who succumbed to neoplastic disease not associated with cachexia. The adrenal weights ranged from 11.93 to 14.41 Gm, averaging 12.46 Gm.

## ATHEROSCLEROSIS

Eleven cases of atherosclerosis are included in the series. Seven of the patients were males and 4 were females. The average age of this group was 65 years. The combined adrenal weight averaged 11.6 Gm. Five pairs weighed less than 10.50 Gm, 5 ranged between 12.60 and 13.84 Gm, and only 1 pair weighed as much as 16 Gm. On microscopic examination the striking feature was the normal histologic appearance of 6 of the 11 pairs of glands. The weights of these 6 normal-appearing pairs of glands averaged approximately 10 Gm. Two other pairs exhibited a slight degree of focal depletion of lipid in the outer part of the zona fasciculata. The remaining 3 showed an increase in the lipid of the inner part of the zona fasciculata.

the average weight is 13.4 Gm. The more striking depletion of cortical lipid is seen in cases of acute infectious diseases of the most fulminating type (fig. E).

Infectious diseases are not the only conditions in which such changes in the adrenal glands are known to occur. They have been described by Landau,<sup>15</sup> Albrecht and Weltmann<sup>26</sup> and Hueck<sup>27</sup> in various neoplastic diseases. Ball and Samuels<sup>29</sup> demonstrated adrenal enlargement in animals with experimentally produced tumors. These authors suggested that the enlargement might in some way be attributed to the extreme breakdown of necrotic tumor tissue. In the present series it is apparent that while cancer per se is associated with slight enlargement of the adrenal glands without significant alteration in the cortical lipid content, the more striking adrenal enlargement associated with marked depletion of lipid is found in those cases of cancer which are complicated by cachexia.

In addition to infectious diseases and malnutrition with their attendant metabolic disorders, other pathologic conditions may be associated with adrenal enlargement and depletion of lipid. The latter include pemphigus, eczema, extensive burns and protracted vomiting. It can be seen that all of these conditions, associated with marked dehydration and depletion of chlorides, throw an increased demand on the adrenal glands. Illustrative examples follow.

A 79 year old man had had acute pemphigus for four months. The skin and the mucous membranes were the site of most extensive denudations. A terminal rise in the blood nonprotein nitrogen occurred. The adrenal glands together weighed 15.80 Gm and the widened cortex exhibited marked depletion of lipid. Adrenal changes like those just described have been observed in man after extensive burns (Kolosko,<sup>30</sup> Napp,<sup>31</sup> Albrecht and Weltmann<sup>26</sup>) and have been experimentally reproduced by Pfeiffer,<sup>32</sup> Nakata<sup>33</sup> and Niemeyer.<sup>34</sup> Kamniker<sup>35</sup> noted similar changes in a child dying with extensive eczema.

Protracted vomiting was the chief symptom in the next case. The patient was a 58 year old woman suffering from high intestinal obstruction. After four days of persistent emesis, she was admitted to the hospital in profound shock associated with dehydration. She died twelve hours after admission. Her adrenal glands weighed 17.12 Gm, and the widened cortex showed depletion of lipid.

Similar changes were observed by Wohl and his co-workers<sup>36</sup> following experimental high intestinal obstruction. Treatment with large amounts of extract of adrenal cortex was found by these authors to prolong markedly the period of survival after experimental ligation of the jejunum.<sup>37</sup> Scudder and his associates<sup>38</sup> reported elevation of serum potassium in experimental intestinal obstruction.

29 Ball, H. A., and Samuels, L. T. Adrenal Weights in Tumor-Bearing Rats. *Proc. Soc. Exper. Biol. & Med.* **38**: 441, 1938.

30 Kolosko, A. Ueber Befunde an den Nebennieren bei Verbrennungstod, *Vrtljschr. f. gerichtl. Med.* (supp. 1) **47**: 217, 1914.

31 Napp, O. Ueber den Fettgehalt der Nebenniere, *Virchows Arch. f. path. Anat.* **182**: 314, 1905.

32 Pfeiffer, H. Ueber Veränderungen des Nebennierenorgans nach nervösen und toxischen Störungen, *Ztschr. f. d. ges. exper. Med.* **10**: 1, 1920.

33 Nakata, T. Das Verhalten der Nebenniere und Milz bei Verbrennung mit besonderer Berücksichtigung der Todesursache, *Beitr. z. path. Anat. u. z. allg. Path.* **73**: 439, 1925.

34 Niemeyer, R. Ueber Nebennierenveränderungen bei experimentellen Vergiftungen und bei Verbrühungen, *Ztschr. f. d. ges. exper. Med.* **14**: 346, 1921.

35 Kamniker, K. Beitrag zur Kenntnis der Nebennierenblutungen, *Frankfurt Ztschr. f. Path.* **35**: 487, 1927.

36 Wohl, M. G., Burns, J. C., and Clark, J. H. Adrenal Gland in Dogs with High Intestinal Obstruction, *Proc. Soc. Exper. Biol. & Med.* **33**: 543, 1936.

37 Wohl, M. G., Burns, J. A., and Pfeiffer, G. High Intestinal Obstruction in the Dog Treated with Extract of Adrenal Cortex. *Proc. Soc. Exper. Biol. & Med.* **36**: 549, 1937.

38 Scudder, J., Zwemer, R. L., and Truszkowski, R. Potassium in Acute Intestinal Obstruction, *Surgery* **1**: 74, 1937.

of other newborn infants, i. e. a fat-free outer part of the zona glomerulosa, a dense band at the junction of the zona glomerulosa and the zona fasciculata, a sparse distribution of fine sudanophilic material in the zona fasciculata, and an increased concentration of lipid in the zona reticularis. This lipid pattern was in contradistinction to that described by Liebegott<sup>18</sup> and Benecke<sup>19</sup>. They found the outer half of the cortex free of lipid and the inner part of the zona fasciculata and the zona reticularis heavily laden with this material. It should be stated that only in 1 case in the series were extramedullary foci of hemopoiesis found.

#### COMMENT

From the study of the available material it has become apparent that distinct morphologic changes occur in the cortex of the adrenal gland in various pathologic conditions— inflammatory diseases, hypertension and malnutrition. The morphologic alterations consist of an increase in the size of the glands associated with various degrees of depletion of the lipid in the cortex. On the basis of Hass-phenylhydrazine stain employed with selected human adrenal glands, it seems reasonable to conclude that the sudanophilic material present in the cortex represents in part the adrenocortical steroids. Hence, the morphologic changes described in the cortex take on physiologic significance, lending themselves to functional interpretations.

Adrenal cortical changes in infectious diseases as described in the foregoing paragraph were known to Fraenkel<sup>20</sup> (grip), Thomas<sup>21</sup> (scarlet fever and diphtheria), Dietrich<sup>22</sup> and Goormaghtigh<sup>23</sup> (*Bacillus welchii* infections). Deucher<sup>24</sup> as well as Dietrich observed similar alterations in acute peritonitis. Kawamura<sup>25</sup>, Albrecht and Weltmann,<sup>26</sup> Hueck,<sup>27</sup> and Wulfig<sup>28</sup> described depletion of cortical lipoids as a general feature of infectious diseases. I am able to confirm the changes in the amount and the arrangement of the sudanophilic substance in the cortex as well as the increase in the size of the gland in various infectious diseases. Also borne out in the present study is Wulfig's statement that the adrenocortical changes are not specific and that their intensity depends on the duration and the virulence of the infections. The average combined adrenal weight in cases of acute inflammatory disease is 15.47 Gm. whereas in cases marked by chronicity

18 Liebegott, G., in discussion on Bleumer, H. Glycogenspeicher Krankheit Verhandl. d. deutsch. path. Gesellsch. **31** 18, 1938.

19 Benecke, E. Hyperinsulinismus und Glykogenspeicherung beim Icterus familiaris gravis, Zentralbl. f. allg. Path. u. path. Anat. **72** 401, 1939.

20 Fraenkel, E. Ueber die blutgefässschädigende Wirkungen des Grippeerregers, Zentralbl. f. allg. Path. u. path. Anat. **33** 104, 1923.

21 Thomas, E. Ueber die Nebennieren der Kinder und ihre Veränderungen bei Infektionskrankheiten, Beitr. z. path. Anat. u. z. allg. Path. **50** 283, 1911.

22 Dietrich, A. Die Nebennieren bei den Wundinfektionskrankheiten, Zentralbl. f. allg. Path. u. path. Anat. **29** 169, 1918.

23 Goormaghtigh, N. Sur le fonctionnement de la capsule surrénale humaine dans les gangrènes gazeuses, Compt. rend. Soc. de biol. **81** 14, 1918.

24 Deucher, G. Veränderungen der Nebennierenrinde bei Peritonitis und Sepsis, Arch. f. klin. Chir. **125** 578, 1923.

25 Kawamura, D. Die Cholesterinester-Verfettung, Jena, Gustav Fischer, 1911.

26 Albrecht, H., and Weltmann, O. Ueber das Lipoid der Nebennierenrinde, Wien. klin. Wchnschr. **24** 483, 1911.

27 Hueck, E. Ueber experimentell erzeugte Veränderungen im Lipoidgehalt der Nebennierenrinde und ihre Beziehungen zum Cholesteringehalt des Blutes, Verhandl. d. deutsch. path. Gesellsch. **15** 251, 1912.

28 Wulfig, M. Die Veränderungen der Nebennierenrinde bei Infektionskrankheiten, Virchows Arch. f. path. Anat. **253** 239, 1924.

observed following acute starvation (Jackson<sup>47</sup>, Mulinos and Pomerantz<sup>48</sup>, Sarason<sup>49</sup>) as well as the feeding of a diet rich in protein (Engel and Tepperman<sup>50</sup>, Sarason<sup>49</sup>). Whitehead<sup>51</sup> described cortical proliferation in the adrenal glands of mice after injections of peptone. These are all instances of accelerated protein catabolism. The marked adrenal enlargement associated with depletion of lipid in cachectic patients may be explained on the basis of increased breakdown of body protein. Engel and Tepperman<sup>50</sup> stated that an increase in protein catabolism is often the underlying factor in various diverse conditions known to be associated with adrenal hypertrophy. Coincident with this accelerated breakdown of tissue protein there is liberation of intracellular potassium. It seems not unlikely, therefore, that the adrenal changes observed in those clinical conditions associated with profound disturbances of electrolyte and protein metabolism are the manifestations of increased demands made on the adrenal cortex.

While this paper serves to emphasize changes of the adrenal cortex secondary to metabolic disturbances associated with systemic disease, it must not be forgotten that the disease itself may directly involve the adrenal glands giving rise to symptoms of adrenal insufficiency. Hemorrhage, infarction and necrosis of the adrenal gland occurring in the course of severe infectious diseases have been emphasized by Thomas,<sup>21</sup> Oberndorfer,<sup>52</sup> Hutinel,<sup>53</sup> Fraenkel,<sup>20</sup> Kovacs,<sup>54</sup> Furuta,<sup>55</sup> Simmonds,<sup>56</sup> Goldzieher<sup>57</sup> and others. In the present series they were not a prominent feature and did not exceed an occasional focal miliaary extravasation of red blood cells. Mention should be made, however, of the case of a 61 year old man who, two hours after an injection of bromsulfalein, showed a rise in temperature and signs and symptoms of shock. (The dye used was from a lot which has caused marked febrile reactions in other patients.) The state of shock terminated in death after eighteen hours. The autopsy disclosed massive bilateral adrenal hemorrhages with necrosis of cortex and medulla associated with thrombus formation in the large veins. No inflammatory disease was found anywhere in the body. This is in contrast to the so-called Waterhouse-Friederichsen syndrome, which consists of bilateral hemorrhagic infarction of the adrenals associated with septicemia, particularly meningococcemia. Virchow<sup>58</sup> mentioned 2 cases of sudden death of previously healthy persons in which the only pathologic change was hemorrhagic infarction of the adrenal glands.

47 Jackson, C M. Effects of Acute and Chronic Inanition upon the Relative Weights of the Various Organs and Systems of Adult Albino Rats, *Am J Anat* **18** 15, 1915

48 Mulinos, M G, and Pomerantz, L. Hormonal Influences on Weight of Adrenal in Inanition, *Am J Physiol* **132** 368, 1941

49 Sarason, E L. Morphologic Changes in the Rat's Adrenal Cortex Under Various Experimental Conditions, *Arch Path* **35** 373 (March) 1943

50 Engel, F, and Tepperman, S J. To be published

51 Whitehead, R. Cortical Proliferation in the Mouse Suprarenal After Peptone, *Brit J Exper Path* **13** 200, 1932

52 Oberndorfer, S. Gynakologische Gesellschaft in Munchen, *Munchen med Wchnschr* **52** 777, 1905

53 Hutinel, V. Les lesions des capsules surrenales dans la scarlatine, *Arch f Kinderh* **60-61** 397, 1913

54 Kovacs, J. Beiderseitige akute Nebennierenblutung bei Influenza, *Frankfurt Ztschr f Path* **38** 387, 1929

55 Furuta, S. Morbus Addisonii durch arterielle Embolien der Nebennieren, *Virchows Arch f path Anat* **251** 553, 1924

56 Simmonds, M. Ueber Nebennierenblutungen, *Virchows Arch f path Anat* **170** 242, 1903

57 Goldzieher, M. The Adrenals, New York, The Macmillan Company, 1929

58 Virchow, R. Berliner medicinische Gesellschaft, *Berl klin Wchnschr* **9** 95, 1864

The conclusions concerning the mutual relations of the adrenal cortex and systemic disease are fragmentary and require further documentation. This is illustrated by another case.

A 65 year old woman known to be addicted to the use of alcoholic beverages, suffered from persistent emesis for several months prior to death. On admission to the hospital she was semicomatose, with a blood pressure of 50 systolic. The diastolic pressure was not obtainable. She presented all the signs of peripheral circulatory collapse. The nonprotein nitrogen of the blood amounted to 56 mg per hundred cubic centimeters, and the chlorides were markedly depressed to the level of 60 miliequivalents. Despite the administration of blood and saline solution, she never recovered from shock, dying in forty-eight hours. At autopsy no cause of death could be demonstrated. It was generally agreed that the electrolyte disturbance was responsible for her death. The adrenal glands were enlarged weighing 16.35 Gm. In contrast with the adrenal cortex in the first cited case of vomiting the cortex in this instance contained abundant lipid.

It should be emphasized that all of the aforementioned conditions including infectious diseases, pemphigus, eczema, burns and protracted vomiting, are associated with signs and symptoms of adrenal insufficiency of varying degree. Moreover, death in the conditions enumerated may at times be attributed to adrenal insufficiency. The lowering of blood chlorides in infectious disease is well known (Peters and Van Slyke<sup>39</sup>). Changes in the electrolyte pattern of the blood characteristic of adrenal insufficiency have been described by Talbot and his co-workers<sup>40</sup> in pemphigus and by Stoesser<sup>41</sup> in infantile eczema. Talbot stated that administration of large amounts of extract of adrenal cortex resulted in correction of the electrolyte disturbance and simultaneous clinical improvement. Maclean,<sup>42</sup> Nitschke and Kratschell<sup>43</sup> and Stenger<sup>44</sup> found elevation of serum potassium and depression of serum chlorides, associated with hemoconcentration in cases of severe burns and infectious diseases.

As can be seen from the foregoing citations the literature contains extensive reference to the pathologic alteration of the adrenal glands. The emphasis, however, has been on the direct effect of various pathologic conditions on these glands. The changes secondary to metabolic disturbances associated with disease have not been adequately considered.

The adrenal glands are recognized by all to be intimately concerned with water, electrolyte, protein and carbohydrate metabolism. Recent papers point to the important role of these glands in protein metabolism. Long and his co-workers<sup>45</sup> demonstrated that adrenocortical compounds furthered the conversion of body protein to carbohydrate. It has been shown recently by Levin and Leatham<sup>46</sup> that the decrease in serum albumin following hypophysectomy may be corrected by administration of desoxycorticosterone acetate. Adrenal hypertrophy has been

39 Peters, J. P., and Van Slyke, D. D. *Quantitative Clinical Chemistry*. Baltimore, Williams & Wilkins Company 1931, vol. 1.

40 Talbot, J. H., Lever, W. F., and Consolazio, W. B. *Metabolic Studies on Patients with Pemphigus*, *J. Invest. Dermat.* **3** 31, 1940.

41 Stoesser, A. V. *Potassium Chloride Therapy and Serum Potassium in Infantile Eczema*, *Proc. Soc. Exper. Biol. & Med.* **49** 332, 1942.

42 Maclean, A. *The Suprarenal Glands in Diphtheria*, *J. Hyg.* **37** 345, 1937.

43 Nitschke, A., and Kratschell, B. *Blutveränderungen bei der toxischen Diphtherie und ihre Beziehung zum Nebennieren-Ausfall*, *Klin. Wchnschr.* **17** 374, 1938.

44 Stenger, K. *Blutveränderungen bei schweren Infektionskrankheiten und bei Verbrennungen. Ihre Beziehung zur Nebennierenschädigung*, *Klin. Wchnschr.* **18** 576, 1939.

45 Long, C. N. H., Katzin, B., and Fry, E. G. *Adrenal Cortex and Carbohydrate Metabolism*, *Endocrinology* **26** 309, 1940.

46 Levin, L., and Leatham, J. H. *The Relation of the Pituitary, Thyroid and Adrenal Glands to the Maintenance of Normal Serum Albumin and Globulin Levels*, *Am. J. Physiol.* **136** 306, 1942.

# Progress in Internal Medicine

## DISEASES OF THE HEART

A REVIEW OF SIGNIFICANT CONTRIBUTIONS MADE DURING 1942

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WITH THE EDITORIAL ASSISTANCE OF PAUL D WHITE, MD

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### ANATOMY, PHYSIOLOGY AND METHODS

Beginning with the thesis that there must be full agreement between the structure and the function of the heart, Robb and Robb<sup>1</sup> have briefly, yet cogently, correlated the results of certain anatomic and physiologic studies. They point out that anatomists have repeatedly demonstrated that the ventricles of mammalian hearts are made up of discrete muscle bands and that the origin, the course and the attachments of these separate muscles are also fairly well known. These views, however, are not compatible with the assumption, held by many investigators that the whole heart is one syncytium. If this were absolutely true, the Robbs point out, the findings of the anatomists would have to be considered artefacts. Further proof of the view that the cardiac musculature is indeed composed of distinct muscles is seen in (1) the specific functions of the several ventricular muscles, (2) the individual blood supply of each and (3) the fact that injury may be localized to a particular muscle and that such injury produces a constant and characteristic change in the electrocardiograms of various animals. Further proof is looked for from work in progress designed to show (1) whether the sheaths surrounding the muscle bands extend throughout their course, and (2) whether there are in fact specialized conduction pathways with a distribution similar to that of the Purkinje tissue in ungulates.

Richards and his associates<sup>2</sup> found that the average right auricular pressure in 6 normal human subjects was plus 37 mm of water. Direct measurements of venous pressure were made by introducing a catheter into the right auricle and locating the position of the tip by means of roentgen rays. Their findings are of particular interest because it has long been assumed (on the basis of experiments in animals) that the average right auricular pressure is zero or slightly less. Richards and associates further found that the average gradient from arm to heart was plus 41 mm of water in normal subjects, whereas in 3 patients with congestive heart failure the pressures in the vein of the arm and the right auricle were almost the same.

Cournand, Ranges and Riley<sup>3</sup> have tested the accuracy of the ballistographic method of determining cardiac output by comparing it with a method (involving

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The opinions and views set forth in this article are those of the writer and are not to be considered as reflecting the policies of the United States Navy Department.

1 Robb, J. S., and Robb, R. C. The Normal Heart. *Anatomy and Physiology of the Structural Units*, *Am Heart J* **23** 455, 1942.

2 Richards, D. W., Jr., Cournand, A., Darling, R. C., Gillespie, W. H., and Baldwin, E. DeF. Pressure of Blood in the Right Auricle, in Animals and in Man. Under Normal Conditions and in Right Heart Failure, *Am J Physiol* **136** 115, 1942.

3 Cournand, A., Ranges, H. A., and Riley, R. L. Comparison of Results of the Normal Ballistocardiogram and a Direct Fick Method in Measuring the Cardiac Output in Man, *J Clin Investigation* **21** 287, 1942.



Josue,<sup>59</sup> Landau,<sup>15</sup> Albrecht and Weltmann,<sup>20</sup> Hueck<sup>27</sup> and Thomas<sup>60</sup> described adrienal enlargement with increased storage of lipid in contracted kidneys. The marked increase in the weight of the adrienal glands associated with lipid storage in nephrosclerosis (average weight, 15.9 Gm.) and the less marked enlargement in hypertension following chronic glomerulonephritis and pyelonephritis (average weight, 13.5 Gm.) are difficult to explain. These findings corroborate those recently reported by Rinehart and his co-workers<sup>61</sup> in similar cases of hypertension. The latter authors suggested "hypersecretion of the adrienal cortex may in some cases be a factor in the genesis of what is now classified as essential hypertension."

The enlargement of the adrienal glands in hypertension is in contrast to the normal weight (average, 11.6 Gm.) and normal histologic appearance of the glands in atherosclerosis of the large arteries. These findings conflict with those reported by Hueck<sup>27</sup> and others.

Leibegott<sup>18</sup> and more recently Durlacher<sup>62</sup> demonstrated increased storage of glycogen in the myocardium of infants dying with erythroblastosis foetalis. Quantitative chemical analysis (Durlacher) and Best's carmine stain have been employed to show the increase in cardiac glycogen. The disturbance in carbohydrate metabolism in erythroblastosis is very likely correlated with the striking adrienal enlargement. Whether the latter is the result of the faulty carbohydrate metabolism or the primary cause remains to be settled.

#### SUMMARY

The adrienal glands of 110 patients were studied in an effort to correlate cortical changes with systemic disease.

Cortical enlargement associated with depletion of lipid or reversal of lipid pattern was found associated with inflammatory diseases, cachexia, pemphigus and protracted emesis.

Cortical enlargement with an increased amount of lipid was encountered in cases of hypertension, the change was more striking when the hypertension was associated with primary vascular disease. The explanation of these changes is not at hand.

No significant alterations were present in the series of cases of atherosclerosis. Extreme enlargement was found in 4 cases of erythroblastosis foetalis.

This study serves to emphasize that the enlargement of the adrienal cortex and the depletion of lipid are reflections of the metabolic disturbances associated with certain systemic diseases and not the direct effect of the latter.

Dr. Rolf Katzenstein aided in the preparation of this article and in the compilation of the bibliography. Miss Virginia Lane and Mr. Luther Mardiros gave technical assistance.

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59 Josue, O. Capsules surrenales, hypertension arterielle, atherome, *Bull. et mém. Soc. méd. d'hôp. de Paris* **21** 139, 1904.

60 Thomas, E. Ueber Veränderungen der Nebennieren, bei Schrumpfnieren, *Beitr. z. path. Anat. u. z. allg. Path.* **44** 228, 1910.

61 Rinehart, J. F., Williams, O. O., and Cappeller, W. D. Adenomatous Hyperplasia of the Adrenal Cortex Associated with Essential Hypertension, *Arch. Path.* **32** 169 (Aug) 1941.

62 Durlacher, S. H. Unpublished data.

An impressive normal sinoauricular bradycardia has been reported by White <sup>4a</sup> in 4 athletes, 3 of whom were long distance runners. The basal heart rates in the 4 athletes were as follows: a marathon winner, 38, an aviator, 38, a champion miler, 37, and a champion two-miler, 35. Thus, the range of the normal heart rate has been shown to be more extended than previously thought.

#### CARDIAC ARRHYTHMIAS

Wolff <sup>5</sup> has discussed the paroxysmal tachycardias primarily from the standpoint of the clinical manifestations. His series of 125 cases included 81 instances of paroxysmal auricular fibrillation, 24 of paroxysmal auricular tachycardia, 11 of paroxysmal auricular flutter and 9 of paroxysmal ventricular tachycardia. Various types of heart disease were represented in varying grades of severity. There were, in addition, 25 instances in which the heart was normal. Wolff found that the significant variables include the ventricular rate (and in a lesser degree the type of rhythm), the underlying heart disease, the cardiac reserve, the sensitiveness of the patient and the presence or the absence of embolism. A ventricular rate of 150 a minute was found to be critical, below this rate symptoms are not often provoked unless embolism complicates the paroxysm, whereas at rates above 150 symptoms are usually induced regardless of all other variables. The type of rhythm is significant chiefly because of the association of different types with certain forms of heart disease. The nature and the severity of the underlying heart disease have an important influence on the symptoms. Patients with mitral stenosis in whom a paroxysm of rapid tachycardia develops become dyspneic, and pulmonary edema and hemoptysis may occur. Patients who experience angina on effort suffer similarly during paroxysms unless the rate is under 150. In patients with congestive failure or greatly limited cardiac reserve the onset of a paroxysm, especially if rapid and prolonged, may precipitate gross congestive failure. Even here, however, the heart rate is a critical factor, because at rates much below 150 no aggravation of signs or symptoms is noted. Wolff agrees that heart failure may occur in persons with normal hearts as a result of a paroxysm of rapid tachycardia but hints that this is not common save in infants and children. In 41 of Wolff's 125 cases symptoms were not provoked, all types of tachycardia were represented as well as various types and stages of heart disease.

Cooke and White <sup>5a</sup> have published a study of paroxysmal tachycardia and paroxysmal auricular fibrillation, consisting of an analysis of 750 cases encountered in the cardiographic laboratory at the Massachusetts General Hospital from 1928 to 1938. They concluded that when the cardiovascular system is normal, attacks of paroxysmal tachycardia are uncomfortable but relatively unimportant incidents, without effect on longevity, but that the occurrence of an attack in a patient seriously ill must be regarded with apprehension, and the occurrence of heart failure as the result of an attack may lead to the formation of intracardiac thrombi and subsequent emboli.

In a second paper <sup>5b</sup> these same authors discussed 27 cases of ventricular paroxysmal tachycardia, 24 of which were found in a review of electrocardiograms.

4a White, P. D. Bradycardia (Below Rate of 40) in Athletes, Especially in Long Distance Runners, Correspondence, *J. A. M. A.* **120** 642 (Oct. 24) 1942.

5 Wolff, L. Clinical Aspects of Paroxysmal Rapid Heart Action, *New England J. Med.* **226** 640, 1942.

5a Cooke, W. T., and White, P. D. Prognosis of Paroxysmal Tachycardia and Paroxysmal Auricular Fibrillation, *Brit. Heart J.* **4**:153, 1942.

5b Cooke, W. T., and White, P. D. Paroxysmal Ventricular Tachycardia, *Brit. Heart J.* **5** 33, 1943.

catheterization of the right auricle) based on the Fick principle. They found that with the latter method the cardiac output was 18.5 per cent greater than the value calculated from the ballistocardiogram with Bazett's tables for the internal cross section of the aorta. However, when diodrast was used for visualization in determining aortic cross section, the two methods checked very closely, the average difference being 3.5 per cent. They suggest, therefore, that with respect to absolute accuracy the ballistocardiographic method may be improved either by making a correction of 18.5 per cent or by using diodrast in the determination of the aortic cross section.

Rappaport and Sprague<sup>4</sup> have discussed in a comprehensive manner the graphic registration and interpretation of normal heart sounds. They point out that an observer using an ordinary stethoscope does not hear the cardiac sound vibrations as they actually are because of three major forms of distortion:

1 The heart sounds are modified in their path of travel from the source to the surface of the chest.

2 The vibrations that reach the surface of the chest are further modified by the stethoscope and type of chest piece employed.

3 The human hearing mechanism (that is, the ear, the nervous pathways, and the brain) additionally modifies the heart sound vibrations.

Phonocardiographic registration may also be considered in the light of the same modifications or distortions, with the types being defined as follows:

a Linear phonocardiography, or the registration of the sound vibrations as they exist on the surface of the chest.

b Stethoscopic phonocardiography, or the registration of the sound vibrations as they are transmitted to the ears by an average acoustic stethoscope.

c Logarithmic (human audiographic) phonocardiography, or the registration of sound vibrations as they are perceived by a competent observer if the personal factors are omitted.

The advantages of each type in the analysis of the heart sounds are clearly outlined, as well as the advantages of a simultaneous recording of the venous pulse.

Their observations indicate that the first heart sound comprises four components, the second and third of which are ordinarily heard in auscultation:

a The first, which is caused by residual vibrations of auricular origin.

b The second, which is produced at the beginning of the isometric contraction phase of the cardiac cycle (closure of the mitral and tricuspid valves).

c The third, which is caused by the opening of the semilunar valves.

d The fourth, which is caused by the acceleration of the blood in the arterial vessels during the maximum ejection phase of ventricular systole.

The second heart sound also comprises four components, of which only the second is heard in auscultation:

a The first vibrations, which represent the beginning of the diastolic fall in pressure with ventricular relaxation.

b The second group of vibrations, which are caused by the closure of the semilunar valves (termination of ventricular systole).

c The third group, which are most likely due to the arterial wall and blood column vibrations. An additional possible source of vibration in this phase of the second heart sound may be the natural period vibration of the chest wall, which may conceivably be set into oscillation by the second component.

d The fourth component is caused by the opening of the mitral and tricuspid valves.

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4 Rappaport, M. B., and Sprague, H. B. The Graphic Registration of the Normal Heart Sounds, *Am Heart J* 23: 591, 1942.

paralleled the gravity of the cardiac lesion" In a group of 97 normal subjects with premature beats, on the other hand, alternation for more than three beats following the premature beat "was never observed, except for transitory and minimal alternation in 3 subjects with tachycardia" The authors present their evidence that palpitation occurring with premature beats is not due to the extra large beat which follows but to the premature beat itself They point out that when the onset of ventricular systole occurs prematurely and at a time when rapid diastolic inflow is still continuing and the auriculoventricular valves are widely separated, the cusps are brought together more forcibly than normal so that the intensity of the first sound is increased, and that with this there may be consciousness of the heart beat

Perera, Levine and Erlanger,<sup>8</sup> prompted by the clinical impression that patients with bundle branch block of the right type have a better prognosis than do those with the left type, were able to confirm this impression by an analysis of 104 cases of right bundle branch block They found that the average survival time after the diagnosis of right bundle branch block was three years for 29 patients who died and four years and one month for 62 patients remaining alive Thirteen patients could not be traced They found that the prognosis for life was one year and two months for 60 patients with left bundle branch block, which is in accord with the experience of most other investigators

White and Blumgart<sup>9</sup> have reported 2 cases which are of considerable interest in the further appraisal of the use of quinidine in the treatment of certain cardiac arrhythmias They point out that although the appearance of embolic phenomena during the course of auricular fibrillation is generally regarded as a contraindication to the use of quinidine, yet in certain cases, as exemplified in a patient of theirs, the restoration of normal rhythm may result in the cessation of embolism A further example is given of the use of quinidine in restoring normal rhythm in a patient with active rheumatic infection, congestive failure and auricular fibrillation in whom digitalis failed to control adequately the ventricular rate The use of quinidine, ordinarily thought to be contraindicated in the presence of rheumatic fever and congestive failure, was considered to be life saving

#### ELECTROCARDIOGRAPHY

*Genesis of the Electrocardiogram*—During the past few years there has accumulated an impressive body of knowledge serving to cast doubt on the validity of Einthoven's equilateral triangle hypothesis These investigations and the controversies surrounding them have been of small concern to those primarily interested in clinical electrocardiography, since Einthoven's hypothesis seemed to serve for all practical purposes However, the recent work of Wolferth, Livezey and Wood<sup>10</sup> stands in contradiction to this hypothesis and, more important, the methods used point the way to possible new advantages of a clinical nature

They have shown that the pattern of potential variations along radial lines extending, roughly, from the heart to the tip of each shoulder, does not change significantly except for decrement as the distance from the heart increases By pairing appropriate areas along these lines they obtained a series of tracings closely resembling lead I On the right side the deflections ("C-1 pattern") were relatively large near the heart in the C<sub>1</sub> area (fourth intercostal space to the right of

8 Perera, G. A., Levine, S. A., and Erlanger, H. Prognosis of Right Bundle Branch Block, *Brit Heart J* 4:35, 1942

9 White, P. D., and Blumgart, H. L. Cessation of Repeated Pulmonary Infarction and of Congestive Failure After Termination of Auricular Fibrillation by Quinidine Therapy, *J Mt Sinai Hosp* 8:1095, 1942

10 Wolferth, C. C., Livezey, M. M., and Wood, F. C. Studies on the Distribution of Potential Concerned in the Formation of Electrocardiograms *Am J M Sc* 203:641, 1942

taken on 25,000 patients in the cardiographic laboratory of the Massachusetts General Hospital from 1914 to 1929. They established the following four criteria for diagnosis:

- 1 The presence of P waves at a slower rate than that of abnormal QRS waves during a paroxysm of tachycardia
- 2 A paroxysm of abnormal ventricular complexes, i. e., three or more, occurring during auricular fibrillation
- 3 The onset of tachycardia with an abnormal ventricular complex
- 4 Close resemblance of the complexes of ventricular premature beats to the complexes occurring during paroxysmal tachycardia

Coronary heart disease was present in 22 of the 27 cases, in 4 other cases the heart was apparently normal, and in 1 it was thought to have a congenital ventricular defect. There were 17 males and 10 females, the youngest being aged 18 years and the oldest 81 years. Digitalis had been administered to 13 of the 27 patients before the onset of the tachycardia and was probably the chief etiologic factor in at least 5 of them. The prognosis was generally but not always poor. Only 2 patients with coronary heart disease survived longer than two years after the first attack, 5 patients with hearts otherwise normal had survived to the date of writing, the periods varying from two to fifteen years.

Rosenbaum, Johnston and Keller<sup>6</sup> have described in detail their findings in 2 cases of paroxysmal ventricular tachycardia in childhood and have briefly summarized the 7 other definite cases previously reported. In 3 of the 9 cases there was no associated cardiac abnormality, while in the remaining 6 there was congenital or acquired heart disease. In 7 of the 9 cases there were important symptoms associated with the paroxysms (slowest ventricular rate, 192), including abdominal pain, dyspnea, nausea and vomiting, anorexia and pain in the chest. In 1 case there were no associated symptoms, but the paroxysms were short, and in the remaining case there were repeated bouts of fever associated with the tachycardia. The authors stress the importance of accurate diagnosis and the value of adequate doses of quinidine sulfate in restoring normal rhythm.

Ungerleider and Gubner<sup>7</sup> have written an interesting report of their observations on premature beats and the mechanism of palpitation. Electrocardiograms were obtained on 1,142 applicants for life insurance who were found to have premature beats on clinical examination, in 58 per cent there was no evidence of heart disease. Among the factors which were found to increase the significance of premature beats were:

- 1 The occurrence of premature beats of multifocal origin
- 2 Frequent and persistent premature beats, particularly if they occur successively in short runs interrupting the regular rhythm
- 3 A definite increase in the number or shower of extrasystoles immediately following exercise
- 4 Occurrence of premature contractions in the presence of a rapid heart rate
- 5 Inversion of the T wave in the regular beat which follows the extrasystole
- 6 Post-extrasystolic pulsus alternans

The last-named factor refers to the occurrence of temporary pulsus alternans following the premature beat, which is probably due to left ventricular strain. This was observed in 21 of 42 cases of heart disease, "and the degree of alternation

6 Rosenbaum, F. F., Johnston, F. D., and Keller, A. P. Paroxysmal Ventricular Tachycardia in Childhood, *Am J Dis Child* **64**: 1030 (Dec) 1942.

7 Ungerleider, H. E., and Gubner, R. Extrasystoles and the Mechanism of Palpitation, *Tr Am Therap Soc* **41**: 1, 1942.

*Influence of Posture, Drugs, Exercise and Other Factors on the Electrocardiogram*—White and his colleagues<sup>13e</sup> have reported the finding of an inversion of the T waves in lead 2 of the electrocardiogram as a normal physiologic variation in occasional persons, particularly those of asthenic habitus with vertical hearts and with a tendency toward neurocirculatory asthenia. The position of the heart was the most important factor in producing this inversion of the T waves, which was found in the sitting or the standing position and was corrected by recumbency or by an elevation of the diaphragm such as that at full expiration. Autonomic nervous influences comprise another factor, less striking as a rule. The relatively common normal occurrence of inversion of the T waves in lead 2 makes imperative that one recognize it in order to avoid an erroneous diagnosis of heart disease.

Mayerson and Davis<sup>14</sup> have described the changes in the electrocardiogram of a normal subject when the latter is passively tilted from the horizontal to the upright (75 degree) position. They believe the initial changes are due to a shift in the position of the heart and to alterations in its contact with neighboring tissues but that the later changes are due primarily to increased sympathetic activity occasioned by the decreased venous return and consequent relative cerebral anoxia. Mayerson and Davis do not believe the electrocardiographic changes they observed are due to anoxemia of the myocardium as do some authors. The outstanding changes observed were an increase in the amplitude of P in leads 2 and 3, a decrease in the amplitude of T in all leads, a shift of the average QRS axis to the right and of the average T axis to the left, and a decrease in the QRST area. Stewart and Bailey<sup>15</sup> have described the variations in the form of the chest leads with change in position and found that as the subject's posture was changed from supine to sitting, to lying on the left side, the outstanding changes consisted of a decrease in the amplitude of the R and T waves, which varied concordantly, and in many cases a decrease in the amplitude of the S waves.

Hartwell and his associates<sup>16</sup> found that exercise, epinephrine, atropine and acetylbetamethylcholine chloride (mecholyl chloride) all had a tendency to lower the T waves of the electrocardiogram, while ergotamine increased the amplitude of T. Pettus and his co-workers<sup>17</sup> found no characteristic changes in electrocardiograms following the administration of large doses of morphine to normal subjects and to patients with heart disease. Geiger and his collaborators<sup>18</sup> found that a significant lowering or inversion of the T waves of the electrocardiogram occurred during or shortly after massive arsenotherapy, with a return to the normal within a few weeks. Stewart and Smith<sup>19</sup> observed various arrhythmias and changes in the T waves and RST segments as a result of the administration of potassium salts.

13e White, P. D., Chamberlain, F. L., and Graybiel, A. Inversion of the T Waves in Lead II Caused by Variation in the Position of the Heart, *Brit Heart J* **3** 233, 1941.

14 Mayerson, H. S., and Davis, W. D., Jr. The Influence of Posture on the Electrocardiogram, *Am Heart J* **24** 593, 1942.

15 Stewart, H. J., and Bailey, R. L. The Effect of Posture on the Form of Precordial Leads of the Electrocardiogram, *Am Heart J* **18** 271, 1939.

16 Hartwell, A. S., Burrett, J. B., Graybiel, A., and White, P. D. Effect of Exercise and of Four Commonly Used Drugs on Normal Human Electrocardiogram, with Particular Reference to T Wave Changes, *J Clin Investigation* **21** 409, 1942.

17 Pettus, W. W., Geiger, A. J., and Grzebien, T. Effects of Morphine on the Electrocardiogram of Man, *Yale J Biol & Med* **14** 493, 1942.

18 Geiger, A. J., Craige, B., Jr., and Sadusk, J. F., Jr. Observations on the Massive Dose Arsenotherapy of Early Syphilis by the Intravenous Drip Method. II. Electrocardiographic Abnormalities Associated with Massive Arsenotherapy, *Yale J Biol & Med* **14** 357, 1942.

19 Stewart, H. J., and Smith, J. J. Changes in the Electro-Cardiogram and in the Cardiac Rhythm During the Therapeutic Use of Potassium Salts, *Am J M Sc* **201** 177, 1941.

the sternum) but became progressively smaller as the tip of the shoulder was approached. On the left side the deflections ("C-5 pattern") were relatively large near the heart in the C<sub>1</sub> area (fifth intercostal space in the left anterior axillary line) but became smaller as the left shoulder tip was approached. Because lead 1 represents the subtraction of the C<sub>1</sub> from the C<sub>5</sub> pattern, which are chiefly derived from different parts of the heart, and after each has undergone decrement, it seems reasonable to suppose that the study of the C<sub>1</sub> and C<sub>5</sub> patterns separately should prove valuable. Wolfarth and his associates admittedly have made only a beginning with this new method but its possible advantages seem very important.

Nahum, Hoff and Kaufman<sup>11b</sup> have now reported observations on the nature of the Q and S waves. These observations form part of a more extended work, previously reported,<sup>12</sup> on the genesis of the normal and of the abnormal electrocardiogram in experimental animals. They found that the downstroke of Q<sub>1</sub> is produced by early electrical activity in the anterior surface of the left ventricle and the upstroke by electrical activity in the posterior surface of the right ventricle, while the downstroke of Q<sub>3</sub> is produced by early electrical activity in the posterior surface of the left ventricle and the upstroke by excitation of the anterior surface of the right ventricle. The downstroke of S<sub>3</sub> develops with the complete activation of the posterior surface of the left ventricle while a portion of the anterior surface of the right ventricle is not yet active, and the upstroke of S<sub>1</sub> occurs when the remainder becomes active and restores isopotentiality. S<sub>1</sub> probably arises from a similar sequence of excitation in the anterior surface of the left and the posterior surface of the right ventricle. These findings are wholly in accord with their previous observations that lead 1 is formed by the summation of the anterior levocardiogram and the posterior dextrocardiogram and lead 3 by the summation of the anterior dextrocardiogram and posterior levocardiogram.

*Fetal Electrocardiography*—The recording of the electrocardiogram of the fetus has passed from the stage of medical curiosity to that of practical clinical application. Recent studies<sup>13</sup> have shown that by the use of proper technics fetal electrocardiograms may be obtained from the fourth month until the end of pregnancy. The obtaining of records earlier in pregnancy, desirable though this may be, is not likely to prove successful because of the shielding effect of the membranes and the amniotic fluid. The percentage of positive results increases with the length of pregnancy, and in the last month failures are rare. The curves do not have the same configuration as those from adults, and interpretation is made still more difficult because of artefacts. Nevertheless a number of measurements can be made. Fetal hearts generally show sinus arrhythmia and may show extrasystoles and varying degrees of heart block. There is little change in the fetal heart rate from the fourth month to the end of pregnancy, and there is no correlation between the fetal heart rate and the maternal heart rate or the sex of the fetus. This method is useful in the clinical study of effects of various drugs and procedures on the fetal heart.

11 (a) Hoff, H. E., Nahum, L. H., and Kaufman, W. The Nature of Q-1 and Q-3, *Am J Physiol* **135** 752, 1942. (b) Nahum, L. H., Hoff, H. E., and Kaufman, W. The Nature of the S Complex of the Electrocardiogram, *ibid* **136** 726, 1942.

12 Graybiel, A., and White, P. D. Diseases of the Heart. A Review of Significant Contributions Made During 1941, *Arch Int Med* **70** 303 (Aug.) 1942.

13 (a) Goodyer, A. V. N., Geiger, A. J., and Monroe, W. M. Clinical Fetal Electrocardiography, *Yale J Biol & Med* **15** 2, 1942. (b) Bernstein, P., and Mann, H. A Clinical Evaluation of Fetal Electrocardiography, *Am J Obst & Gynec* **43** 21, 1942. (c) Mann, H., and Mayer, M. D. The Uterine Electrocardiogram, *J Mt Sinai Hosp* **8** 805, 1942. (d) Ward, J. W., and Kennedy, J. A. The Recording of the Fetal Electrocardiogram, *Am Heart J* **23** 64, 1942.

patients with congenital heart disease should be evaluated in much the same fashion as other cardiac patients so far as pregnancy is concerned. To this general rule they make two exceptions: (1) Pregnancy in patients with coarctation of the aorta is attended by so great a risk that it should be avoided or interrupted, and (2) special precautions should be taken with patients in whom there exists the possibility of a reversal of an arteriovenous shunting of blood.

Prinzmetal<sup>22</sup> has described an ingenious method for determining whether or not a venous-arterial shunt is present in patients with congenital heart disease and the approximate magnitude of the shunt. One-half cubic centimeter of a 50 per cent solution of ether is injected into the antecubital vein with a needle of large bore (14 to 16 gage), and the interval between the time of injection and the moment the patient feels a prickly burning sensation in the face is recorded. In the absence of a venous-arterial shunt this facial sensation is not experienced because all the ether is eliminated by the lungs. In the event a shunt has been demonstrated, the observer injects a 50 per cent solution of saccharin, beginning with 0.1 cc and successively increasing the dose by 0.1 cc until the smallest amount which the patient can taste is determined. If 50 per cent or more of the circulating blood enters the shunt, the "saccharin time" will approximate the "ether time." If the former is considerably longer than the latter, it can be concluded that more than half of the blood goes through the regular channel, and the approximate percentage can be calculated as follows. Inject successively larger amounts of saccharin until the point is reached at which the circulation time suddenly becomes shorter. This indicates that the injection is large enough to permit a detectable quantity of saccharin to reach the tongue by way of the shunt. The approximate volume of the shunt ( $K$ ) can be determined by means of the formula  $K = \frac{a}{a-c}$  in which  $a$  is the smallest amount of saccharin which can be tasted in the longer circulation period and  $c$  the smallest amount of saccharin that can be tasted in the shorter period.

*Coarctation of the Aorta*—Stewart and Bailey<sup>23</sup> have reported their studies on 14 patients with coarctation of the aorta. The cardiac output was measured in 9 of the patients, and the output per square meter of body surface was found to be increased in 4 (2.85 to 3.45 liters), normal in 4 (1.93 to 2.10 liters) and decreased in 1 (1.61 liters). The basal metabolic rate was increased in 3 of the 9 patients, but the circulation time was not shortened as it is in patients with hyperthyroidism. The circulation time was within or near normal limits above the level of coarctation but was prolonged below this level in most instances. It is of interest that the most constant of the characteristic signs of coarctation was a higher systolic blood pressure in the arms than in the legs. The one exception to this rule was observed in a patient with only slight narrowing at the site of coarctation, whose condition was not diagnosed during life. Stewart and Bailey confirm the finding of Steele that the increase in peripheral resistance need not be confined to the upper half of the body but may be generalized and that under these circumstances so far as the distribution of peripheral arteriolar resistance is concerned, the arterial hypertension in coarctation of the aorta does not differ from the common forms of arterial hypertension.

*Patent Ductus Arteriosus*—The cure of bacterial infection superimposed on patent ductus arteriosus represents a dramatic achievement. The results of Touroff

22 Prinzmetal, M. Calculation of the Venous-Arterial Shunt in Congenital Heart Disease, *J Clin Investigation* 20:705, 1941.

23 Stewart, H. J., and Bailey, R. L., Jr. The Cardiac Output and Other Measurements of the Circulation in Coarctation of the Aorta. *J Clin Investigation* 20:145, 1941.



## CARDIOVASCULAR ROENTGENOLOGY

Comeau and White<sup>19a</sup> have made a critical analysis of the standard methods of estimating the size of the heart from roentgen measurements. Their most important conclusion is that the range of size of the normal heart is great and has not yet been adequately determined in roentgen studies. More suitable standards for comparison with the area of the roentgen heart shadow than height, weight and body surface are needed, and probably measurements of body build of one kind or another will eventually help to solve the problem. The authors state that a comparison of the transverse diameters, the frontal areas and the volumes of 200 normal hearts (150 from males and 50 from females) leads one to conclude that the transverse diameter of the heart compares favorably with the other actual cardiac measurements and is the most satisfactory from the clinical standpoint. The application of cardiac transverse diameters to prediction tables by the use of the Hodges-Eyster figures is recommended with a view to discarding the other measurements, such as the cardiothoracic ratio. The measurement of the frontal area, although fairly satisfactory, was found less suitable, since it is not so completely an objective measurement. Prediction tables for the transverse diameter based both on orthodiographic and teleroentgenographic measurements are now available.

## CONGENITAL HEART DISEASE

Gelfman and Levine<sup>20</sup> have determined the incidence of bacterial endocarditis and endarteritis in cases of congenital heart disease based on an analysis of 34,023 autopsy protocols in four large hospitals of Boston. There were 453 cases (1.3 per cent) of congenital heart disease, of which 6.6 per cent showed superimposed bacterial infection. However, 272 (60 per cent) of the 453 congenitally abnormal hearts were from patients who died before the age of 2 years, and a complicating cardiac bacterial infection had developed in only 5 of these. The incidence of bacterial endocarditis in the remaining 181 cases was found to be 16.6 per cent, and these cases are separately considered as follows. Bacterial infection was not present in any cases of interauricular septal defect but was present in 42 per cent of all and 57 per cent of the uncomplicated cases of interventricular septal defect, in 28 per cent of all and 20 per cent of the uncomplicated cases of patent ductus arteriosus, in 21.2 per cent of cases of bicuspid aortic valves, in 29 per cent of cases of pulmonary stenosis and in 28.6 per cent of cases of the tetralogy of Fallot. It is of interest that 25 of the 181 cases of congenital defect were complicated by rheumatic infection, and subacute bacterial endocarditis was present in 8 of these 25 and was solely on the site of the rheumatic lesion in 5.

Mendelson and Pardee<sup>21</sup> have reported their experience with 20 pregnant patients who had congenital heart disease. The 20 cases formed 1.89 per cent of 1,089 instances of organic heart disease in approximately 31,000 obstetric cases. The particular defects in these cases were labeled as follows: pulmonary stenosis in 8 cases, interventricular septal defect in 4, coarctation of the aorta in 3, patent ductus arteriosus in 2, patent foramen ovale in 1, congenital defect, unclassified in 2. Only 1 patient had congestive failure during pregnancy, the remaining 19 did not appear to suffer any ill effects. From a review of the previously reported cases as well as their own, Mendelson and Pardee conclude that

19a Comeau, W. J., and White, P. D. A Critical Analysis of Standard Methods of Estimating Heart Size from Roentgen Measurements, *Am J Roentgenol* **47** 665, 1942.

20 Gelfman, R., and Levine, S. A. The Incidence of Subacute Bacterial Endocarditis in Congenital Heart Disease, *Am J M Sc* **204** 324, 1942.

21 Mendelson, C. L., and Pardee, D. E. B. Congenital Heart Disease During Pregnancy, *Am J M Sc* **202** 392, 1941.

ular axis is such that the left auricle occupies a definitely more cephalad position than the right. Further, the plane of the foramen ovale (septal defect) is almost horizontal, and not vertical as it is commonly represented. With the disposition of the chambers and the septal defect in this relation, filling of the right auricle is accomplished by the usual caval flow and by a gravitational flow through the communication in the floor of the superiorly placed left auricle. Dilatation of the right auricle results, and, in due time, the right side of the heart shows dilatation and hypertrophy, whereas the left auricle and ventricle, which play almost no role in these events, remain essentially unaffected. The aorta becomes hypoplastic because of the decreased systemic volume of blood. The pulmonary arterial tree, on the other hand, necessarily dilates to accommodate the increased volume of blood in the lesser circuit. The presence of mitral stenosis simply exaggerates the flow differences.

#### RHEUMATIC HEART DISEASE

The most important recent advance with respect to rheumatic heart disease is the piling up of evidence that recrudescences may be prevented by the use of one or other of the sulfonamide drugs. It may almost be stated as a fact that recurrences of rheumatic activity may be prevented in over 90 per cent of those so treated and that the natural history of the disease, as a consequence, may undergo a substantial change.

Kuttner and Reyersbach<sup>28</sup> have carried out a careful study, the results of which confirm the fact that streptococcic infections of the upper respiratory tract and rheumatic relapses in rheumatic children are prevented by the prophylactic administration of sulfanilamide. Their studies were carried out during two successive winters on rheumatic children living in an institution. There was every facility for daily clinical observation and routine bacteriologic studies.

The 108 rheumatic children were carefully divided into two groups matched as closely as possible with regard to age, sex, number of previous rheumatic attacks and cardiac findings. Beginning in October and continuing until the following June, those in one group received daily doses of sulfanilamide. During the first winter, 1 to 2 Gm (depending on weight) was given in divided doses, and an average blood level of 2 mg per hundred cubic centimeters was maintained. During the second winter the dose was slightly less, and the average blood level was 1.5 mg per hundred cubic centimeters.

During the first winter 30 of the 54 children in the control group contracted pharyngitis due to group A hemolytic streptococcus type 15. Following a latent period varying from three to twenty-one days, 14 of these 30 had definite rheumatic recurrences, and an additional 4 had questionable recurrences. In contrast to this, only 1 child in the treated group contracted pharyngitis due to the type 15 streptococcus, the administration of the drug was continued, and no rheumatic sequelae developed.

During the second winter 17 children in the control group of 50 presented pharyngitis due to an unidentified type of group A hemolytic streptococcus. Following a latent period varying from ten to eighteen days, 9 of these 17 children had definite rheumatic recurrences and 1 a questionable recurrence. Only 1 child in the control group had pharyngitis due to the same organism and, following a latent period, mild rheumatic manifestations.

Toxic reactions developed in 15 per cent of the children receiving the drug, the others tolerated the drug well.

<sup>28</sup> Kuttner, A., and Reyersbach. The Prevention of Upper Respiratory Infections and Rheumatic Recurrences in Rheumatic Children by the Prophylactic Use of Sulfanilamide, *J Clin Investigation* **22** 77, 1943.

and his associates<sup>21</sup> indicate that following the ligation of the ductus cure is the rule and failure to cure the exception. Similarly good results have been obtained by others who have followed Touroff's lead, and additional reports may be expected soon.

The extraordinary feature of this treatment is that simple ligation of the ductus should result in cure of the bacterial infection. The vegetations are rarely confined to the ductus, and even when they are, ligation or division of the ductus would not remove all of the vegetations or destroy all of the bacteria. Touroff,<sup>24</sup> in describing the effects of operation, speculates on this matter. He points out that after occlusion of the ductus healing of vegetations presumably occurs as a result either of the alteration of local mechanical factors or of changes in nutrition or of both. One theory is that the organisms die because they no longer enjoy the protection of the fibrin which was continuously precipitated by the action of swirling currents of blood. Another theory is that the growth of organisms in the ductus and the pulmonary artery is favored by the high oxygen content of the shunted blood and that an adequate supply of oxygen is lacking after the shunt is closed. It may be pointed out, however, that *Streptococcus viridans* infection may complicate other types of congenital defects in which the oxygen saturation of the arterial blood is low.

Further reports<sup>25</sup> on the operative cure of uncomplicated patent ductus arteriosus continue to show good results.

*Interauricular Septal Defect*—Tinney and Barnes<sup>26</sup> have presented the findings in 4 additional cases of interauricular septal defect, 2 of which were complicated by mitral stenosis. One of the latter was further complicated by subacute bacterial endocarditis, and at necropsy a large vegetation was found directly in the interauricular septum. For some reason subacute bacterial endocarditis is an extraordinarily rare complication in cases of interauricular septal defect, this being the second recorded instance, even here the primary lesion may have been on the mitral valve, as this too was involved.

Uhley<sup>27</sup> has presented a new concept of the dynamics of interauricular septal defect based on a correlation between hydraulic principles and anatomic considerations. He criticizes the current view that preponderant dilatation and hypertrophy of the right ventricle and auricle are caused by shunting of blood through the communication, which in turn results from higher pressure in the left than in the right auricle. Uhley reviews the anatomic evidence showing that the auric-

24 (a) Touroff, A. S. W. The Rationale of Operative Treatment of Subacute Bacterial Endarteritis Superimposed on Patent Ductus Arteriosus, *Am Heart J* **23** 847, 1942, (b) Blood Cultures from the Pulmonary Artery and Aorta in a Patient with Infected Patent Ductus Arteriosus, *Proc Soc Exper Biol & Med* **49** 568, 1942. (c) Touroff, A. S. W., and Tuchman, L. E. Subacute *Streptococcus Viridans* Endarteritis Superimposed on Patent Ductus Arteriosus. Spontaneous Recovery. Recurrence After Twelve Years, Recovery Following Surgical Treatment, *Am Heart J* **23** 857, 1942. (d) Touroff, A. S. W., Vesell, H., and Chasnoff, J. Operative Cure of *Streptococcus Viridans* Endarteritis Superimposed on Patent Ductus Arteriosus. Report of the Second Successful Case, *J A M A* **118** 890 (March 14) 1942.

25 Johnson, J., Jeffers, W. A., and Margolies, A. The Technique of the Ligation of the Patent Ductus Arteriosus, *J Thoracic Surg* **11** 347, 1942. Bourne, G. Changes in Renal Function and Persistence of the Murmur After Ligation of Patent Ductus Arteriosus, *Brit Heart J* **3** 228, 1941. Dolley, F. S., and Jones, J. C. The Surgical Treatment of Persistently Patent Ductus Arteriosus, *Brunn, Med-Surg Tributes*, 1942, p. 123. Nixon, J. W. Ligation of the Patent Ductus Arteriosus. Successful Case, *Surgery* **12** 31, 1942.

26 Tinney, W. S., and Barnes, A. R. Interauricular Septal Defect, *Minnesota Med* **25** 637, 1942.

27 Uhley, M. H. Lutembacher's Syndrome and a New Concept of the Dynamics of Interatrial Septal Defect, *Am Heart J* **24** 315, 1942.

They found that rest in bed for a year or more results in a significant decrease in the size of the heart, that bradycardia (1 case) resulted in a slight but definite enlargement and that tachycardia up to rates of 180 to 200 produced no change in size but that rates over 200 may result in considerable cardiac enlargement if long continued. Keith and Brick then studied the changes in the size of the heart during the various stages of a single attack of rheumatic fever in 100 patients. From two to twelve roentgenograms were taken on each patient, and the cardiac surface area on admission was compared with that when progressive change had ceased to occur. They found that in 33 of the patients the heart became larger, in 18 it remained unchanged and in 49 it became smaller. If the patients with pericarditis are left out, the average increase was 8 sq cm, which was approximately the same as the average decrease, which was 9 sq cm. The time required for the maximal change to occur was approximately the same (over five months) whether the heart became larger or smaller, indicating that the change is not a sudden process. They found that the heart muscle shows greater recuperative powers than the heart valves and that valvular damage may occur without enlargement of the heart. Criteria are presented which should aid in the differential diagnosis of cardiac dilatation and pericarditis with effusion and carditis and valvulitis.

#### BACTERIAL ENDOCARDITIS

*Streptococcus Viridans Endocarditis*—Hundreds of patients with *Str. viridans* endocarditis have been treated with one or other of the sulfonamide drugs and sometimes with one of these drugs in combination with heparin, dicoumarin, hyperthermia or typhoid vaccine. Probably all or nearly all of the cures are reported, while many of the failures are not. If consideration is given to the possible error in diagnosis, the rare spontaneous recovery and the possibility of late relapse (some of the cures have not been followed for long), the treatment, though more effective than in the days before the introduction of the sulfonamide compounds, is still disappointing. The high percentage of cures reported by Smith, Sauls and Stone<sup>33</sup> from a review of the literature does not provide an adequate picture. The experience of some investigators suggests that none of the various adjuncts to chemotherapy as yet reported are of proved value or, at least, to be relied on, though further studies are indicated. The single very favorable exception is in patent ductus arteriosus, in which ligation of the ductus forms part of the treatment.<sup>34</sup>

A rational approach to chemotherapy has been presented by Orgain and Poston,<sup>35</sup> who find not only that there are a large number of viridans strains but that there

Independent Factors in Auricular Mural Thrombus Formation, *Am Heart J* **24** 1, 1942. (d) Cohn, A. E., and Lingg, C. The Natural History of Rheumatic Cardiac Disease, *Mod Concepts Cardiovasc Dis*, 1942, vol 11, no 7. (e) Console, A. D. The Relation of Cardiac Lesions to Clinical Course of Rheumatic Fever, *Arch Int Med* **69** 551 (April) 1942. (f) Juster, I. R. The Relationship of Upper Respiratory Infections to Rheumatic Activity in Chronic Rheumatic Heart Disease, *Ann Int Med* **16** 1137, 1942. (g) Burgess, A. M., and Ellis, L. B. Chest Pain in Patients with Mitral Stenosis, with Particular Reference to So-Called "Hypercyanotic Angina," *New England J Med* **226** 937, 1942.

33 Smith, C., Sauls, H. C., and Stone, C. F. Subacute Bacterial Endocarditis Due to *Streptococcus Viridans*. A Survey of the Present Status of the Previously Reported Cures and a Clinical Study of Fifteen Treated Cases, Including Another Cure, *J A M A* **119** 478 (June 6) 1942.

34 Footnotes 24 and 25.

35 Orgain, E. S., and Poston, M. A. Sulfonamide Compounds in Therapy of Bacterial Endocarditis, *Arch Int Med* **70** 777 (Nov.) 1942. Poston, M. A., and Orgain, E. S. A Comparison of the Bacteriostatic Effect of the Sulfonamide Drugs upon the Growth of Twenty-Five Strains of *Streptococcus Viridans*, *Am J M Sc* **203** 577, 1942.

Kuttner and Reysersbach rightly point out that their results indicate not only the effectiveness of sulfanilamide in preventing streptococcal infections of the upper respiratory tract and recurrences of rheumatic fever but that infection with group A hemolytic streptococcus is an important factor in the etiology of rheumatic fever.

Hansen, Platou and Dwan<sup>29</sup> also obtained strikingly good results by administering sulfanilamide or, in a few instances, sulfathiazole (2-[paraaminobenzenesulfonamido]-thiazole) or sulfadiazine (2-[paraaminobenzenesulfonamido]-pyrimidine) to 53 children with rheumatic heart disease from October into June. Only 2 of the 53 treated children experienced a recurrence of rheumatic activity while of the 32 control children 17 experienced 21 recurrences, although there was no difference in the number of infections of the upper respiratory tract in the two groups. These results were in full accord with other clinical features which indicated that the treated group tended to be in better condition.

Coburn and Moore<sup>30</sup> have investigated the prophylactic value of salicylates in preventing rheumatic recurrences. Children with quiescent rheumatic heart disease were asked to report to the clinic at the onset of any attack of pharyngitis, at which time cultures of material from the throat were made, and a daily ration of 4 to 6 Gm of salicylates was begun. If the cultures contained an organism other than group A hemolytic streptococcus, the treatment was discontinued and the patient omitted from the study. All but 1 of 47 patients treated with salicylates escaped clinical manifestations of rheumatic fever while 57 of 139 controls suffered recurrences. The reviewers are not aware of any comparable study showing that the salicylates have any great value in preventing rheumatic recurrences. The advantages of their use, if confirmed, are obvious, especially the advantage that they may be successfully used during or immediately after the first phase (respiratory infection), at which time the sulfonamide compounds are not only valueless but contraindicated.

Wasson and Brown<sup>31</sup> have reported their further studies on immunization against rheumatic fever. Treatment consisted essentially in repeated injections of graduated doses of crude or modified hemolytic streptococcus toxin (N Y 5 strain). Patients so treated and followed over a period of years have had fewer recurrences than controls and, if their disease became active, had less severe symptoms. So far as prevention of recurrences is concerned, this method is more troublesome and the results not so good as when the sulfonamide compounds are given.

There have been a number of articles<sup>32</sup> dealing with various clinical phases of rheumatic fever which are of interest. Of especial importance is the report of Keith and Brick<sup>32a</sup> on the changes in the size of the heart with active rheumatic infection. In preparation for their work with patients suffering from rheumatic fever they observed the effect of rest in bed and of heart rate on normal controls.

29 Hansen, A. E., Platou, R. V., and Dwan, P. F. Prolonged Use of Sulfonamide Compound in Prevention of Rheumatic Recrudescences in Children. Evaluation Based on Four Year Study in Sixty-Four Children, *Am J Dis Child* **64** 963 (Dec.) 1942.

30 Coburn, A. F., and Moore, L. V. Salicylate Prophylaxis in Rheumatic Fever, *J Pediat* **21** 180, 1942.

31 Wasson, V. P., and Brown, E. E. Further Studies on Immunization Against Rheumatic Fever, *Am Heart J* **23** 291, 1942.

32 (a) Keith, J. D., and Brick, M. Changes in the Size of the Heart in Children with Rheumatic Fever, *Am Heart J* **24** 289, 1942. (b) Levine, S. A., and Kauvar, A. J. The Association of Angina Pectoris or Coronary Thrombosis with Mitral Stenosis, *J Mt Sinai Hosp* **8** 754, 1942. (c) Hay, W. E., and Levine, S. A. Age and Auricular Fibrillation as

to point out more than some of the recent advances and the present trend in research. In doing this it is important to separate fact from theory and to keep clearly in mind that there may be important differences between the mechanism of the experimental production of hypertension in animals and the mechanism of its occurrence in man.

*Experimental Hypertension*—There is no reason to doubt that constriction of the renal arteries in various animals may lead to permanent hypertension due to a humoral mechanism of renal origin. There is good evidence that this hypertension is due to the liberation of a substance, renin, which interacts with another substance, renin activator or hypertension precursor, to form the effective vasoconstrictor agent named angiotonin (Page) or hypertensin (Braun-Mendenez).

Goldblatt and his associates<sup>39a, g</sup> have found that an adequate amount of adrenal cortical tissue is necessary for the liberation or formation of renin activator (hypertensin precursor), as it almost disappears from the systemic blood of untreated adrenalectomized dogs but returns following the administration of desoxycorticosterone acetate. Previous observations by Page on adrenalectomy in experimental hypertension led him to conclude that the adrenal glands were not directly concerned. There is general agreement, however, that the action of renin is not affected by hypophysectomy (recently confirmed by Goldblatt and his co-workers<sup>40</sup>), thyroidectomy, pancreatectomy or gonadectomy.

Much evidence has been adduced in the past to the effect that the vasoconstriction produced by angiotonin is similar to that observed in experimental hypertension. The recent observations of Abell and Page<sup>41</sup> confirm this. By means of moat chambers they were able to observe directly the small vessels in rabbits' ears during the development of experimental renal hypertension. They found that the arterioles became permanently constricted, although not sufficiently to obstruct the blood supply. This constriction occurred whether or not the vessels were supplied with nerves and must therefore have been due to the direct action of some substance. Similar arteriolar responses followed the intravenous injection of angiotonin.

It has also been shown that changes in the intrarenal circulation may be similar in experimental hypertension and after the injection of angiotonin. Since the clearance of diodrast may be decreased while clearance of inulin is well maintained, the characteristic change in intrarenal circulation is thought to consist of a decrease in renal blood flow but an increase in pressure in the glomerular capillaries.

It has further been shown that repeated injections of renin lead to progressive decrease in response because of exhaustion of renin activator (or hypertensin precursor). This phenomenon, called tachyphylaxis, has been thoroughly confirmed.

With regard to the reaction of angiotonin with some further substance there is some difference of opinion. Page has postulated a system of angiotonin

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Nephrectomy, *New England J. Med.* **228**:277, 1942. (f) Page, I. H. Nature of Arterial Hypertension, *J. Missouri M. A.* **39**:237, 1942. (g) Goldblatt, H., Kahn, J. R., and Lewis, H. A. Studies on Experimental Hypertension. XVII. Experimental Observations on the Treatment of Hypertension, *J. A. M. A.* **119**:1192 (Aug. 8) 1942.

40 Goldblatt, H., Braden, S., Kahn, J. R., and Hoyt, W. A. Studies on Experimental Hypertension. XVI. The Effect of Hypophysectomy on Experimental Renal Hypertension, *J. Mt. Sinai Hosp.* **8**:579, 1942.

41 Abell, R. G., and Page, I. H. The Reaction of Peripheral Blood Vessels to Angiotonin, Renin, and Other Pressor Agents, *J. Exper. Med.* **75**:305, 1942, Effects of Renal Hypertension on the Vessels of the Ears of Rabbits, *ibid.* **75**:673, 1942.

is a great variation in the susceptibility of each strain to the various sulfonamide drugs. They found that sodium sulfapyridine (monohydrate sodium salt of 2-[paraaminobenzenesulfonamido]-pyridine) exhibited the most marked effectiveness against the greatest number of strains and that preliminary in vitro tests are probably of value in determining the drug of choice.

*Bacterial Endocarditis Due to Organisms Other Than St. Viridans*—A number of interesting cases have been reported<sup>36</sup> in some of which cures were obtained by the use of sulfonamide drugs. Of particular interest are the reports<sup>37</sup> of 2 cases of mycotic endocarditis. Only 6 cases of this condition have thus far been reported in the medical literature, and 5 of the 6 patients were drug addicts (heroin). Contaminated heroin (diacetyl morphine) is considered to be a likely source of infection. Clinically the cases are characterized by rather slow progression with little fever but with development of focal lesions, especially in the brain. Pathologically the vegetations are grafted on scarred or damaged heart valves and are responsible for multiple embolic phenomena. The sulfonamide compounds are of no value.

Goulder and his associates<sup>38</sup> have reported in detail a case of *Salmonella supestifer* endocarditis and have briefly reviewed the 3 previously reported cases. The endocarditis was superimposed on previous damage to the heart valves in 3 cases, due to rheumatic infection in 2 and to syphilitic infection in 1. The clinical course was rapidly progressive in each case and characterized by chills and high fever, prostration, bacteremia and leukocytosis (an unusual finding in uncomplicated *supestifer* bacteremia). Embolic phenomena and changing heart murmurs occurred in 3 of the 4 cases.

#### ARTERIAL HYPERTENSION

The large number of studies reported on the mechanism of arterial hypertension in animals and the clinical counterpart in man do not lend themselves to brief review. For a complete account of the present status of the nature of arterial hypertension and its treatment reference should be made to the various review articles which have appeared during the past year.<sup>39</sup> At this time one cannot hope

36 Glazebrook, A. J., and Thomson, S. Sulfonamide Compounds and Acute Rheumatism. *J. Hyg.* **42** 20, 1942. Keith, H. M., and Heilman, F. R. Subacute Bacterial Endocarditis Due to the Hemolytic *Streptococcus* Lancefield Group G, *Proc. Staff Meet., Mayo Clin.* **17** 358, 1942. Blumberg, N., Heine, W. I., and Lipshutz, J. *Pneumococcus* (Type XXVIII) Endocarditis with Recovery, *J. A. M. A.* **120** 607 (Oct. 24) 1942. Organ, E. S., and Poston, M. A. Mixed Infections in Bacterial Endocarditis, *Am. Heart J.* **23** 823, 1942. Hamburger, M., Jr., Schmidt, L. H., Rueggsegger, J. M., Sesler, C. L., and Grupen, E. S. Sulfonamide Resistance Developing During Treatment of *Pneumococcus* Endocarditis, *J. A. M. A.* **119** 409 (May 30) 1942.

37 Pasternack, J. G. Subacute Monilia Endocarditis, *Am. J. Clin. Path.* **12** 496, 1942. Wikler, A., and others. Mycotic Endocarditis. Report of a Case, *J. A. M. A.* **119** 333 (May 23) 1942.

38 Goulder, N. E., Kingsland, M. F., and Janeway, C. A. *Salmonella supestifer* Infection in Boston. A Report of Eleven Cases with Autopsy Findings in a Case of Bacterial Endocarditis Due to This Organism, and a Study of the Agglutination Reactions in This Infection, *New England J. Med.* **226** 127, 1942.

39 (a) Goldblatt, H., Lewis, H. A., and Kahn, J. R. The Pathogenesis and Treatment of Hypertension. Experimental Observations, in Nelson Loose Leaf Medicine, New York, Thos. Nelson & Sons, 1942. (b) Page, I. H. Studies on the Mechanism of Arterial Hypertension, *J. A. M. A.* **120** 757 (Nov. 7) 1942. (c) Winternitz, M. C. Some Aspects of the Relation of the Kidneys to Cardiovascular Disease, *J. Iowa M. Soc.* **32** 157, 1942. (d) Lewis, H. A., and Goldblatt, H. Studies on Experimental Hypertension, *Bull. New York Acad. Med.* **18** 459, 1942. (e) White, B. V., Durkee, R. E., and Mirabile, C. Renal Hypertension. A Review of Its Status, Including the Report of a Case of Hypertension Relieved After

recent references to such conditions are listed below<sup>47</sup> These conditions probably represent the clinical counterpart of experimental renal hypertension

With respect to essential hypertension, the causal relation to the kidneys is not wholly clear but a concept of the mechanism and of the part the kidneys play has been summarized by Schroeder<sup>48</sup> He begins by pointing out the well known fact that individual susceptibility is an important factor in the development of essential hypertension and that this susceptibility is usually declared by an excessive vascular response to emotional stimuli This "defect" may be hereditary or the result of early environmental influences He then points out that the injection of epinephrine hydrochloride results in prolonged renal vasoconstriction and that psychic stimulation (anxiety) can apparently do the same The possibility therefore exists that often repeated or prolonged psychic stimulation in predisposed persons may cause a sufficient degree of renal ischemia to result in hypertension Such hypertension would be temporary at first but after a time might lead to permanent hypertension as a result of damaging the renal arterioles Schroeder believes that the foregoing concept may account for the variations in the clinical course so frequently observed

*Treatment of Essential Hypertension in Man*—There is little which is new to report with respect to the treatment of essential hypertension Potassium sulfocyanate continues to enjoy considerable favor despite occasional untoward effects, and it is said to be particularly effective following splachnicectomy Further experience with extracts of kidney tissue have yielded disappointing results, and the general opinion is that these extracts are no more effective than are certain other organ extracts Tyrosinase apparently causes lowering of the blood pressure but not by its enzymatic action, further trial is warranted The most consistently good results have been obtained following splachnicectomy with use of the newer technics In properly selected cases the results are indeed gratifying, and work carried out by Smithwick in Boston, as yet unpublished, has already achieved important results

#### CORONARY HEART DISEASE

*Precipitating Factors of Myocardial Infarction*—All cardiologists agree that myocardial infarction may be precipitated by certain specific events, but there is wide disagreement with regard to the nature of some of these events and the frequency of their occurrence This question is of great and immediate clinical importance for at least two reasons (1) the desire properly to advise patients known to have or suspected of having coronary heart disease how best to avoid cardiac infarction and (2) the medicolegal aspects concerned in the relation of

47 Simonds, J P Renal Pathologic Changes in Hypertension and Glomerulonephritis, J A M A **120** 89 (Sept 12) 1942 Braasch, W F Surgical Kidney as Etiologic Factor in Hypertension, Canad M A J **46** 9, 1942 Fishberg, A M Hypertension Due to Renal Embolism, J A M A **119** 551 (June 13) 1942 Farrell, J I, and Young, R H Hypertension Caused by Unilateral Renal Compression, *ibid* **118** 711 (Feb 28) 1942 Hoffman, B J Renal Ischemia Produced by Aneurysm of Abdominal Aorta, *ibid* **120** 1028 (Nov 28) 1942 Wilson, C L, and Chamberlain, C T Unilateral Renal Ischemia Associated with Hypertension, J Urol **47** 421, 1942 Baerøe, K Hypertension as Result of Renal Ischemia in Dissecting Aneurysm of Aorta, Nord med (Norsk mag f lægevidensk) **12**:3408, 1941 Prinzmetal, M, Hiatt, N, and Tragerman, L J Hypertension in a Patient with Bilateral Renal Infarction Clinical Confirmation of Experiments in Animals, J A M A **118** 44 (Jan 3) 1942 Friedman, B, Moschkowitz, L, and Marrus, J Unilateral Renal Disease and Renal Vascular Changes in Relation to Hypertension in Man, J Urol **48** 5, 1942 Everett, H S, and Scott, R B Possible Etiologic Role of Gynecologic Lesions in Production of Hypertension, Am J Obst & Gynec **44** 1010, 1942

48 Schroeder, H A "Essential" Hypertension A Concept of Its Mechanism, Am J M Sc **204** 734, 1942



activators and inhibitors, while Braun-Mendenez, Fasciolo and others believe that hypertensin is destroyed by a substance of the nature of an enzyme which is present in normal serum and which they named hypertensinase. That the kidneys are the main source of this inhibitor of angiotonin (or hypertensinase) is shown by the fact that after bilateral nephrectomy the inhibitor tends to disappear from the blood. This is consistent with other evidence that the normal kidney elaborates a substance which reduces blood pressure.

Despite the fact that the normal kidney tends to counteract the hypertensive effect of a contralateral ischemic kidney, the results of treating experimental hypertension by means of renal extracts are uncertain. The technical difficulties in separating fractions which may have a specific physiologic effect are great, and final opinion must await further trial. Wakerlin and his associates<sup>42</sup> have reported some success in the treatment of experimental hypertension by the injection of renin, thereby stimulating the production of "antirenin," but others<sup>43</sup> have failed to confirm their findings.

Another approach has been made to the possible role of the kidneys in hypertension by Bing and Zucker (previously reviewed), who have shown that the ischemic kidney is capable of transforming amino acids, themselves without pressor activity into the corresponding amines, which have a strong pressor action. In line with this supposition that phenolic amines may be important factors in renal hypertension, Schroeder and Adams<sup>44</sup> found that tyrosinase will destroy angiotonin because tyrosinase is a phenolic oxidase, Schroeder<sup>45</sup> has suggested that angiotonin may contain a phenolic group. It was found that preparations of tyrosinase from mushrooms were effective in lowering the blood pressure not only in animals but in man. That this effect is due to enzymatic activity is questionable in view of the recent observations of Prinzmetal and his associates<sup>46</sup> that heat-inactivated tyrosinase preparations are as effective as active ones in reducing blood pressure in patients with hypertension. It appears likely that the mechanism of the reduction of blood pressure following the administration of the renal extracts and of tyrosinase is no different from that observed following the injection of typhoid vaccine.

*Role of the Kidneys in Arterial Hypertension in Man*—There is no doubt that a wide variety of pathologic conditions which have in common a partial reduction of blood flow to one or both kidneys may cause permanent hypertension in man. Such conditions include narrowing of the mouths of renal arteries, aberrant renal arteries, various nephritides, chronic atrophic pyelitis and hydronephrosis. Some

42 Wakerlin, G. E., and Johnson, C. A. Reductions in Blood Pressures of Renal Hypertensive Dogs by Hog Renin, *Proc Soc Exper Biol & Med* **46** 104, 1942. Wakerlin, G. E., Johnson, C. A., Smith, E. L., Moss, W. G., and Weir, J. R. Prophylactic Treatment of Experimental Renal Hypertension with Renin, *Am J Physiol* **137** 515, 1942. Wakerlin, G. E., and Johnson, C. A. Antiserum for Renin, *Proc Soc Exper Biol & Med* **44** 277, 1942.

43 Friedman, M., Kruger, H. E., and Kaplan, A. Inability of Purified Renin to Reduce the Blood Pressure of Hypertensive Dogs, *Proc Soc Exper Biol & Med* **50** 56, 1942. The Inability of Purified or Crude Kidney Extract (Renin) to Reduce the Blood Pressures of Hypertensive Dogs, *Am J Physiol* **137** 570, 1942.

44 Schroeder, H. A., and Adams, M. H. Effect of Tyrosinase upon Experimental Hypertension, *J Exper Med* **73** 531, 1941.

45 Schroeder, H. A. Effect of Tyrosinase on Arterial Hypertension, *Science* **93** 116, 1941.

46 Prinzmetal, M., Alles, G. A., Margoles, C., Kayland, S., and Davis, D. S. Effects on Arterial Hypertension of Heat-Inactivated Tyrosinase Preparations, *Proc Soc Exper Biol & Med* **50** 288, 1942.

per cent, a fall in systolic blood pressure (20 mm or more) in 74 per cent, an elevation of venous pressure in 76 per cent, significant electrocardiographic alterations in 86 per cent, leukocytosis in 96 per cent, tachycardia (rate over 80) in 98 per cent, increased sedimentation rate in 98 per cent and fever in every instance. With respect to the last four signs, elevation of the sedimentation rate was the last to occur (third day) but persisted the longest. A rectal temperature above 104 F, a white blood cell count higher than 25,000 or a venous pressure over 200 mm of water indicated a grave prognosis, 7 of 8 patients showing one or another of these signs died within sixteen days after the onset of the attack.

With regard to the immediate mortality in cases of acute myocardial infarction, Levine<sup>52</sup> rightly points out that the figures usually given are from series of cases seen in general hospitals and by consultants, which are apt to be more serious than those commonly seen in general practice. The immediate mortality (death within several weeks) was 33 per cent in Levine's series and 47 per cent in that of Woods and Barnes<sup>53</sup>, Levine believes that the mortality might well prove to be 20 per cent or less if a truly representative series of cases were analyzed. Both Levine and Woods and Barnes agree that age is the most important factor influencing the immediate mortality and that there is little or no difference whether the infarction is in the anterior or in the posterior wall of the heart. Sex is not a very important factor if age is taken into account. The prognosis was found to be better if the electrocardiographic changes were slight (Levine) and much worse in cases in which the position of the infarct could not be localized (Woods and Barnes). The latter workers believe that ventricular extrasystoles are likely to be followed by ventricular tachycardia and not infrequently by ventricular fibrillation, but Levine did not find "simple extrasystoles" to be very important. All agree, however, that the more serious arrhythmias affect the prognosis unfavorably. Other unfavorable factors which Levine mentions are hypertension, fall of blood pressure, especially to levels below 80 mm, pericarditis and congestive failure. He found, as did Shillito and his co-workers,<sup>54</sup> that a high fever, a rapid heart rate and a high white blood cell count are likewise unfavorable factors.

With respect to the ultimate prognosis, Levine<sup>52</sup> found that the average survival period of patients who recovered from their initial attack of myocardial infarction was forty-one and one-tenth months for 101 patients who were known to be dead and twenty-seven and six-tenths months for 271 patients who were found to be still living. The age of the patient was one of the most important factors, the younger patients lived longer. Sex was also very important, the average survival time for women was only eighteen and three-tenths months, compared with forty-three and one-tenth months for men. There was no difference with respect to those who had infarctions of the anterior wall and those who had infarctions of the posterior wall. Of the 80 patients whose mode of death was known, 40 per cent died of a subsequent attack of coronary thrombosis, 35 per cent died instantly, 20 per cent died of congestive failure and only 5 per cent succumbed to causes unrelated to the heart. Levine found that in no less than 75 per cent of 354 cases a return to partial or full duty for an appreciable time was possible.

*Infarction of the Auricles of the Heart*—Cushing and his associates<sup>54</sup> have reported their clinical and experimental observations on auricular infarction.

52 Levine, S. A. The Prognosis of Coronary Occlusion. Part I and Part II. Ultimate Prognosis, *Mod Concepts Cardiovasc Dis*, 1942, vol 11, nos 5 and 6.

53 Woods, R. M., and Barnes, A. R. Factors Influencing Immediate Mortality After Acute Coronary Occlusion, *Am Heart J* 24 4, 1942.

54 Cushing, E. H., Feil, H. S., Stanton, E. J., and Wartman, W. B. Infarction of the Cardiac Auricles (Atria), *Brit Heart J* 4 17, 1942.

accidents to cardiac infarction. To answer the question it is necessary to learn as much as possible of the natural history of this important cardiac complication. Attempts at analyzing the large amounts of clinical data which bear on the problem and to correlate the results of the various authors have proved difficult because of (1) the differences in the nomenclature used, (2) the failure on the part of some to establish the diagnosis of myocardial infarction in the cases reported, (3) the lack of specific criteria or the use of obviously false criteria in attempting to show a causal connection between myocardial infarction and various antecedent events and (4) the desire to bolster this or that theory rather than to seek the truth.

During the past few years much has been written on this subject and a number of articles reviewed. Some recent reports<sup>49</sup> are also of interest. At the present time it seems fair to conclude that myocardial infarction due to coronary thrombosis or to prolonged ischemia in the presence of coronary narrowing without thrombosis may be precipitated by (1) sudden severe effort or prolonged effort of less severity, (2) emotion, particularly if severe or prolonged, (3) various factors which lead to a fall in blood pressure and (4) blows on the chest.

*Clinical Features of Coronary Occlusion and of Myocardial Infarction*—It is well recognized that in a relatively large number of the patients the onset of frank myocardial infarction is preceded by certain premonitory symptoms. These symptoms may be due to the sudden occlusion or narrowing of a coronary vessel without infarction, or if infarction is found, it is small and does not produce the classic symptom complex. Boyer<sup>50</sup> emphasizes the importance of recognizing these prodromal symptoms and the need for instituting immediate and adequate treatment. He illustrates his report with the details of 7 cases which fall into three patterns so far as the symptom of pain is concerned. The first is that of a patient who has pain sufficiently characteristic of coronary occlusion or myocardial infarction but in whom the syndrome of infarction does not at first appear, as a result, some diagnosis other than coronary insufficiency may be made. The second pattern is that of the sudden onset of angina pectoris in a patient previously well, and the third, the sudden increase in severity and frequency of anginal symptoms. In all of these instances the probability of imminent infarction should be considered. Concerning the coronary circulation and the time necessary for the development of collateral circulation, Boyer concludes that two to three weeks of rest in bed, sedation, adherence to a light diet, avoidance of tobacco and possibly papaverine should be prescribed. Not every one will agree with respect to rest in bed, it is the definite impression of some that a little activity is preferable, but the final answer has not been given.

Shillito, Chamberlain and Levy<sup>51</sup> have made a careful study of the cardinal diagnostic features of myocardial infarction in 50 uncomplicated cases seen very early in the attack. A friction rub was heard in 20 per cent, gallop rhythm in 28

49 Boas, E. P. Some Immediate Causes of Cardiac Infarction, *Am Heart J* **23** 1, 1942. Lennoff, H. D. Acute Coronary Thrombosis in Industry. II Indirect Injuries from Toxic Gases and Other Physical Agents, *ibid* **24** 187, 1942. Joki, E., and Suzman, M. M. Mechanisms Involved in Acute Fatal Nontraumatic Collapse Associated with Physical Exertion, *ibid* **23** 761, 1942. Sigler, L. H. Trauma of the Heart Due to Nonpenetrating Chest Injuries, *J A M A* **119** 855 (July 11) 1942. Lennoff, H. D. Acute Coronary Thrombosis in Industry, *Arch Int Med* **70** 33 (July) 1942. Willius, F. A. Cardiac Clinics. Certain Medicolegal Aspects of Coronary Thrombosis, *Proc Staff Meet, Mayo Clin* **17** 521, 1942.

50 Boyer, N. H. Premonitory Symptoms of Myocardial Infarction, *New England J Med* **227** 628, 1942.

51 Shillito, F. H., Chamberlain, F. L., and Levy, R. L. Cardiac Infarction. The Incidence and Correlation of Various Signs, with Remarks on Prognosis, *J A M A* **118** 779 (March 7) 1942.

may be recorded during spontaneous or induced attacks of anginal pain in patients with heart disease. The commonest method of inducing attacks is to ask the patient to exercise and thereby put a greater load of work on the heart. Induced anoxemia has also been used. Neither method found great favor, partly because of the lack of definite criteria in evaluating the results. This objection is being overcome. Recently, Twiss and Sokolow<sup>57</sup> were able to obtain significant electrocardiographic alterations after exercise in 56 per cent of patients with angina pectoris irrespective of the presence or the absence of pain. They found that the significant changes are

S-T segment depression or elevation of 1.0 mm or more in Lead I, of 1.5 mm or more in Lead II, of 1.5 mm or more in Lead III, and 2.0 mm or more in Lead IV, or the conversion of an upright to a diphasic or inverted T wave in Lead I, II, or IV, or the development of bundle branch block. If any one of these changes occurs, the electrocardiogram is considered abnormal.

#### CONGESTIVE HEART FAILURE

A number of interesting articles have appeared dealing with the mechanism of heart failure<sup>58</sup> and the recent developments in treatment.<sup>59</sup>

Boyer and White<sup>59a</sup> have reported 4 instances in which pain in the right upper quadrant of the abdomen, precipitated by exertion and relieved by rest, has been the presenting symptom of early right-sided heart failure. It is evidently due to acute congestion of the liver and is comparable to dyspnea on effort in early left-sided heart failure. Direct questioning of a group of 40 patients who already had clinically evident right-sided failure or were likely candidates for it revealed that the pain had been present at some time in about 45 per cent. It is a symptom to which the patient rarely attaches much significance, since it is usually of little severity and is overshadowed by more uncomfortable symptoms, it is an important though little recognized clue.

*Digitalis Preparations*—Eggleston and Gold<sup>60</sup> have clearly described the extensive changes in the twelfth revision of the United States Pharmacopeia with respect to digitalis.

The greatest uniformity in the strength of digitalis preparations is assured by assaying these preparations against a standard material, the Digitalis Reference

57 Twiss, A., and Sokolow, M. Angina Pectoris. Significant Electrocardiographic Changes Following Exercise, *Am Heart J* **23** 498, 1942.

58 Katz, L. N. Mechanism of Heart Failure, *J Mt Sinai Hosp* **8** 668, 1942. Seymour, W. B., Pritchard, W. H., Longley, L. P., and Hayman, J. M., Jr. Cardiac Output, Blood and Interstitial Fluid Volumes. Total Circulating Serum Protein, and Kidney Function During Cardiac Failure and After Improvement, *J Clin Investigation* **21** 229, 1940. Proger, S., Ginsburg, E., and Magendantz, H. The Effects of the Ingestion of Excessive Amounts of Sodium Chloride and Water on Patients with Heart Disease, *Am Heart J* **23** 555, 1942. Stewart, H. J. Mechanism of Diuresis. Alterations in the Specific Gravity of the Blood Plasma with Onset of Diuresis in Heart Failure, *J Clin Investigation* **20** 1, 1941. Krauel, G. Influence of Nutrition on Circulating Quantity of Blood. Deficient and High Sodium Chloride Content of Diet, *Ztschr f klin Med* **139** 459, 1941. Altschule, M. D., and Zamcheck, N. Studies of the Circulation and Respiration in a Patient with Anasarca Following Administration of Cortin and Sodium Chloride, *J Clin Endocrinol* **11** 269, 1942.

59 Gold, H. Some Recent Developments in Drug Therapy, *North End Clin Quart* **2** 5, 1941. DeGraff, A. C. Evaluation of Drugs Used in the Treatment of Cardiovascular Diseases, *Bull New York Acad Med* **18** 246, 1942. Freedberg, A. S., and Blumgart, H. L. Medical Progress. Digitalis, Edema and Diuretics, *New England J Med* **227** 874, 1942. Gold, H. Recent Developments in Digitalis, *Mod Concepts Cardiovasc Dis*, 1942, vol 12, no 4.

59a Boyer, N. H., and White, P. D. Right-Upper-Quadrant Pain on Effort. An Early Symptom of Failure of the Right Ventricle, *New England J Med* **226** 217, 1942.

60 Eggleston, C., and Gold, H. What the U. S. Pharmacopoeia XII Means to the Physician, *Am J M Sc* **203** 759, 1942.

During a seven year period of investigation, when the auricles at necropsy were specifically examined for infarcts they were found to be involved in 31 (17 per cent) of 182 cases of myocardial infarction. It is remarkable that the infarction involved the right auricle in 27 cases and the left in only 5. Most of the infarcts occurred in the auricular appendages. Gross occlusion of the auricular arteries was observed in only 1 case. However partial or complete occlusion of a main coronary vessel was noted in 23 of the 31 cases, and a fresh or a healed ventricular infarct was present in 22 cases in all of which it was in the left ventricle or the interventricular septum. Acute diffuse myocarditis was present in 2 cases and chronic myocarditis in 1, in the remaining 6 auricular infarcts were the only lesions other than hypertrophy. The gross appearance of the auricular infarcts was similar to that commonly seen in the ventricles and in 26 cases mural thrombi were adherent to the endocardium over the infarcted area.

Electrocardiograms were taken in 23 cases of auricular infarction and in 74 per cent of these the auricular mechanism was abnormal, whereas the auricular rhythm was disturbed in only 8 per cent of 91 cases of ventricular infarction without associated infarction of the auricles. The electrocardiographic abnormalities in the patients with auricular infarcts were auricular fibrillation (9 cases), auricular premature beats (4 cases), auricular flutter (2 cases), sinus arrest (1 case) and wandering pacemaker (1 case). Depression of the PQ level occurred in 5 instances but the authors consider it of doubtful significance because of its occurrence in normal persons. They concluded that an abnormality in the auricular mechanism is the most reliable clue to the clinical diagnosis of infarction of the atriums.

*Angina Pectoris*—Reference is made below to a number of articles<sup>55</sup> dealing with various clinical aspects of angina pectoris. Of particular interest are the reports<sup>56</sup> concerned with the diagnostic value of certain electrocardiographic changes after exercise.

The diagnosis of angina pectoris rests on the subjective phenomenon pain. This pain is not always typical, and the differential diagnosis between pain of cardiac and pain of noncardiac origin may be difficult or even impossible. Approximately one quarter of the patients with angina pectoris show no physical abnormality of the heart by any of the usual methods of examination. Because of this any objective evidence of coronary insufficiency is helpful in diagnosis, it indicates that at least the pain *could* be of cardiac origin. Many investigators over the past few years have shown that significant electrocardiographic alterations

55 Wolferth, C. C., and Edeiken, J. The Differential Diagnosis of Angina Pectoris with Special Reference to Esophageal Spasm and Coronary Occlusion, *Pennsylvania M. J.* **45** 579, 1942. Barnes, A. R., and Pruitt, R. D. Problems in the Differential Diagnosis of Coronary Sclerosis, *J. Michigan M. Soc.* **41** 943, 1942. Heaton, T. G. Conception of Neuralgic Chest Pain, *Canad. M. A. J.* **47** 535, 1942. Elek, S. R., and Katz, L. N. Some Clinical Uses of Papaverine in Heart Disease, *J. A. M. A.* **120** 434 (Oct 10) 1942. Perlow, S. Paravertebral Alcohol Injection for Relief of Cardiac Pain, *Illinois M. J.* **81** 35, 1942. Jones, C. M., and Chapman, W. P. Studies on the Mechanism of the Pain of Angina Pectoris with Particular Relation to Hiatus Hernia, *Tr. A. Am. Physicians* **57** 139, 1942. Lesser, M. A. The Treatment of Angina Pectoris with Testosterone Propionate. Further Observations, *New England J. Med.* **228** 185, 1942. Neuwahl, F. J. Nicotinic Acid in the Treatment of Angina Pectoris, *Lancet* **2** 419, 1942.

56 Scherf, D. Exercise Test in Coronary Stenosis, *Bull. New York M. Coll., Flower & Fifth Ave. Hosps.* **5** 2, 1942. Patterson, J. E., Clark, T. W., and Levy, R. L. A Comparison of Electrocardiographic Changes Observed During the "Anoxemia Test" on Normal Persons and on Patients with Coronary Sclerosis, *Am. Heart J.* **23** 837, 1942. Master, A. M., Dack, S., and Jaffe, H. L. Cardiac Efficiency and Prognosis Following Recovery from Acute Coronary Occlusion. The Results of Various Functional Tests, *J. A. M. A.* **120** 1271 (Dec 19) 1942.

glucoside of *Digitalis lanata*) has the advantages of constant potency and quick action but cannot be used conveniently in ambulatory cases. Lanatoside C, or cecilamid (a crystalline glucoside of *Digitalis lanata*) has the advantages of constant potency and quick action but requires more careful attention with respect to regularity of dosage than do preparations of *Digitalis purpurea* leaf (*digitalis* U S P) and may therefore not be as satisfactory for ambulatory patients.

*Mercurial Diuretics*—The action and the toxicity of the mercurial diuretics have been thoroughly discussed in several articles<sup>64</sup>

An immediate acute reaction characterized by dyspnea and the symptoms of shock has led to death in 26 reported cases. In most of the instances the exact cause of death was thought to be cardiac failure, probably the result of ventricular fibrillation. In each case death occurred following the intravenous administration of the drug. Other types of reaction may result from the toxicity of digitalis owing to the mobilization of this drug in patients previously digitalized and to disturbances of salt and water metabolism. Although all of these possibilities must be kept in mind when one is using the drug, it should be emphasized that toxic reactions are extraordinarily rare and should not limit use of this drug.

#### MISCELLANEOUS

*Isolated Myocarditis*—Occasionally heart failure with fatal termination is observed in a young person for which no cause can be found either during life or at necropsy. Saphir<sup>65</sup> has made an interesting study of 15 such cases which were discovered in the routine examination of 5,626 hearts at autopsy. Clinically, the picture was that of cardiac enlargement and progressive heart failure without obvious cause. Pathologically, Saphir found 1 instance of isolated myocarditis of the granulomatous variety and 14 instances of diffuse myocarditis. The heart with granulomatous myocarditis was not definitely enlarged, and throughout the myocardium there were irregular yellowish white areas. Microscopically, giant cells were observed together with a diffuse infiltration of eosinophils and lymphocytes in the myocardium. Neither spirochetes nor tubercle bacilli could be demonstrated. In 12 of the 14 remaining cases in which clinical data could be obtained the heart was enlarged and dilated. The myocardium was pale gray, with minute grayish streaks or larger areas of gray and white. Microscopically, the lesions were diffuse, with lymphocytes and endothelial leukocytes predominating. These lesions did not resemble those of any clearly defined type of myocarditis.

*Interstitial Myocarditis Due to Sulfonamide Compounds*—French and Weller<sup>66</sup> discovered a significant degree of interstitial myocarditis in 126 of 283 patients who had received one of the sulfonamide compounds (5 to 200 Gm) during the last few weeks of life. Interstitial myocarditis was not present in any patient who had not received chemotherapy for at least thirty days prior to death. The changes observed were not macroscopic but microscopic and were characterized by paravascular cellular infiltrations of eosinophils and other cells. Eosinophilic

64 DeGraff, A. C., and Lehman, R. A. The Acute Toxicity of Mercurial Diuretics, *J. A. M. A.* **119** 998 (July 25) 1942. Kline, E. M., and Seymour, W. B. Systemic Reactions to Mercurial Diuretics, *Am. J. M. Sc.* **203** 874, 1942. DeGraff, A. C., Batterman, R. C., and Lehman, R. A. Limiting Content of Theophylline Necessary to Prevent Local Toxic Action of Mercurial Diuretics, *Proc. Soc. Exper. Biol. & Med.* **38** 373, 1938. DeGraff, A. C., Batterman, R. C., and Lehman, R. A. The Influence of Theophylline upon the Absorption of Mercupurin and Salyrgan from the Site of Intramuscular Injection, *J. Pharmacol. & Exper. Therap.* **62** 26, 1938.

65 Saphir, O. Isolated Myocarditis, *Am. Heart J.* **24** 167, 1942.

66 French, A. J., and Weller, C. V. Interstitial Myocarditis Following Clinical and Experimental Use of Sulfonamide Drugs, *Am. J. Path.* **18** 109, 1942.

Standard of the Pharmacopeia, and 0.1 Gm ( $1\frac{1}{2}$  grains) of this digitalis powder is defined by the Pharmacopeia as 1 U S P unit. The standard powder is supplied by the Pharmacopeia to those who standardize digitalis. The physician may then expect that if he administers 1 U S P unit of digitalis powder or of a tincture of digitalis or of some water-soluble injectable solution, the effects of each in man will be identical, since each will represent the effect of one and the same thing namely 0.1 Gm ( $1\frac{1}{2}$  grains) of the Digitalis Reference Standard. The amount by weight or measure matters little. In one case it might be 2 cc of a solution and in another case 1 cc. What does matter is that the same amount of potent material is administered, and this can be insured by determining dosage in terms of U S P units. For those who have been thinking in terms of cat units it might be stated that 0.1 Gm ( $1\frac{1}{2}$  grains) of the U S P Digitalis Reference Standard or 1 U S P unit will represent approximately 1.3 cat units. In the case of the solutions of ouabain and strophanthin for parenteral administration the dose of the drug is expressed in milligrams, without reference to any unit, and both are assayed against the Ouabain Reference Standard of the Pharmacopeia a pure crystalline material.

Sokolow and his associates<sup>61</sup> have reported their studies on the use of digitalis in the prevention of cardiac failure in patients with sinus rhythm. Four ambulatory patients with sinus rhythm, who had previously shown congestive heart failure were studied for periods varying from thirty-one to sixty weeks. Each was kept on a comparable controlled regimen of activity, salt, fluid and caloric intake. The only variable was the administration or the omission of digitalis. In every instance cardiac failure recurred when digitalis was withheld. They concluded therefore that the administration of digitalis tends to prevent the development of failure in patients with sinus rhythm. Digitalis was also of value in relieving the congestive failure produced in these ambulatory patients by withdrawal of the drug.

Flaxman<sup>62</sup> has made a clinical study of the value of digitalis therapy in patients with heart failure due to hypertension or to coronary arteriosclerosis. He found that digitalis is of great value in treatment even when the rhythm is normal. With both types of patients, digitalis was most effective in those showing isolated failure of the left ventricle and a normal heart rate.

A number of articles<sup>63</sup> have appeared on the use of one or another of the purified glucosides of digitalis. These preparations have been shown to be just as effective as the preparations of digitalis now in common use. Digoxin (a purified

61 Sokolow, M., Weinberg, H. B., Plaut, J. L., and Katz, L. N. Digitalis in the Prevention of Recurrent Cardiac Failure in Patients with Sinus Rhythm, *Ann Int Med* **16** 427, 1942.

62 Flaxman, N. Clinical Value of Digitalis in Hypertensive Heart Failure. I With a Normal Rate and a Regular Rhythm, *Am J M Sc* **203** 741, 1942, II With Sinus Tachycardia, *ibid* **203** 747, 1942, Digitalis in Arteriosclerotic (Coronary) Heart Failure, *J A M A* **119** 252 (May 16) 1942.

63 Rose, O. A., Batterman, R. C., and DeGraff, A. C. Clinical Studies on Digoxin, a Purified Digitalis Glycoside, *Am Heart J* **24** 435, 1942. Gold, H., Kwit, N. T., Cattell, McK., and Travell, J. Studies on Purified Digitalis Glycosides. IV The Single Dose Method of Digitalization, *J A M A* **119** 928 (July 18) 1942. Batterman, R. C., Holman, D. V., and DeGraff, A. C. The Therapeutic Effectiveness and Potency of Digilanid in the Treatment of Congestive Heart Failure, *Ann Int Med* **14** 2058, 1941. Batterman, R. C., Rose, O. A., and DeGraff, A. C. The Combined Use of Ouabain and Digitalis in the Treatment of Congestive Heart Failure, *Am Heart J* **20** 443, 1940. Sokolow, M., and Chamberlain, F. L. Cedilanid with Special Reference to Its Intravenous Use, *ibid* **23** 243, 1942. Chamberlain, F. L., and Sokolow, M. Clinical Experience with the Oral Administration of Cedilanid, and a Comparison of the Oral and Intravenous Preparations of Cedilanid with Digitalis Purpurea, *ibid* **23** 245, 1942. Tandowsky, R. M. Electrocardiographic and Clinical Study of Lanatoside C, *ibid* **24** 472, 1942.

*Heart in Sickle Cell Anemia*—It is thought by some that the cardiac changes in sickle cell anemia are specific, but Klinefelter,<sup>70</sup> on the basis of a careful study of 12 cases, concludes that no cause other than the profound anemia is responsible. Of particular interest are the similarities between the clinical findings in certain cases of sickle cell anemia and those in cases of rheumatic fever. Both may show exacerbations following infection of the respiratory tract, pain and swelling in the joints (which is often migratory), fever and leukocytosis, tachycardia, cardiac enlargement, prolongation of the PR interval in the electrocardiogram, and systolic and diastolic murmurs. They differ among other things in that the pain in sickle cell anemia is often along the bones, that it is not relieved by salicylates and that ulcers of the leg are common in sickle cell anemia.

*Chronic Constrictive Pericarditis*—Harrison and White<sup>71</sup> have analyzed 37 cases of chronic constrictive pericarditis seen by themselves. The later results in 15 of the cases which were reported in 1935 are given, together with a brief clinical survey of the course of illness in 22 additional cases. The ages of the patients ranged from 10 to 59 years. The average age of those operated on was 28.8 years, and the average age of those not operated on was 45.5 years. There were 25 males and 12 females. Tuberculosis was apparently the cause in 5 cases, sepsis in 1, pneumonia with polyserositis in 2, in the other 29 cases the cause was unknown or questionable. In 19, or 54 per cent, of the cases, the cardiac area was enlarged roentgenologically, in 18 the size of the heart was normal. In 9 of the total number of cases there was an apical systolic murmur. In 16, or 43 per cent, there was calcification of the pericardium. The electrocardiogram was abnormal in all cases. The chief abnormalities were low voltage of the QRS waves in all three classical leads in 22, or 60 per cent, of the 37 cases, abnormal T waves of two or three of the classical leads in all cases, auricular fibrillation in 14, or 37 per cent, of the series, and auricular flutter in 1 case. The axis deviation was normal in almost all instances.

Twenty-eight of the 37 patients were treated by pericardial resection. Fourteen of the 28 were clinically cured, although in a few there remained a slight increase in venous pressure above the average normal and 1 of the 14 died of another cause one year after operation. Three other patients were much improved by the operation. Two died primarily of the disease itself, 1 of tuberculosis soon after the operation and 1 in congestion four months after operation. In 5 patients the death was related to the operation, two of the 5 succumbed on the day of operation, 1 died one day after operation, 1 died of pulmonary embolism two days after operation, and 1 died of bronchopneumonia six days after operation. Four died of other complications. Nine patients did not have pericardial resection. In 3 of these the disease was so mild that operation was not thought necessary, 3 were too sick to undergo operation, 1 died of military tuberculosis before the operation could be carried out, 1 died before this series of operations was started, and 1 was lost sight of.

70 Klinefelter, H. F. The Heart in Sickle Cell Anemia, *Am J M Sc* **203** 34, 1942.

71 Harrison, M. B., and White, P. D. Chronic Constrictive Pericarditis. A Follow-Up Study of Thirty-Seven Cases, *Ann Int Med* **17** 790, 1942.



infiltrations were also sometimes observed in the liver, the lungs and the kidneys. Similar eosinophilic interstitial myocarditis was observed in mice and rats receiving daily intraperitoneal injections of sulfonamide drugs. French and Weller point out that the lesions are reversible and that the eosinophilic character make drug idiosyncrasy a likely cause. They emphasize the importance of frequent and careful evaluation of the cardiovascular status of patients receiving sulfonamide drugs.

*Tumors of the Heart*—Beck<sup>67</sup> has published 2 case reports of unusual interest in which he describes the removal of tumors from in and around the heart. The first case was that of a young man 22 years of age who for two years periodically complained of fever, dyspnea, weakness and pain in the chest and had been temporarily relieved after repeated aspiration of fluid, presumably from the pericardium. Because of the persistence of a cystlike structure on the right side of the heart operation was performed and a cyst containing 300 cc. of coagulated material found. It was emptied and washed and the margin of the cyst sutured to the pectoral muscle. The patient improved, but in two years the symptoms recurred and at a second operation a cystic teratoma was found attached to the wall of the heart and great vessels. Beck states, "I had the impression that the wall of the cyst was fused with the parietal pericardium." However, it was not clearly certain from Beck's report that the cyst was intrapericardial. Beck briefly describes 4 other cases previously reported.

Beck's second case was that of a man 39 years of age who complained of progressively increasing dyspnea and pain in the chest on exercise over a period of six years. The clinical studies of Dis Feil and Friedman led to the diagnosis of cardiac tumor. Beck thought that the tumor was probably benign. At operation a large, subepicardial tumor was removed. It consisted of a capsule of calcified connective tissue filled with cheesy material. The patient was well eighteen months after the operation and apparently cured. Beck remarks that this was the first time that a benign tumor of the heart was recognized clinically and the only time that removal was carried out.

*Thiamine Chloride Deficiency and the Circulation*—That cardiac enlargement and failure may result from deficiency of vitamin B<sub>1</sub> is well known and studies along this line are being reported continually.<sup>68</sup> Less well known are the cardiovascular changes resulting from slight or early stages of thiamine deficiency and the time required for their appearance. Johnson and his associates<sup>69</sup> have shown that in healthy persons performing manual labor the signs of vitamin B<sub>1</sub> deficiency may appear in a few days. The reason for the earlier appearance of symptoms in persons doing hard work is that the increased carbohydrate metabolism uses up larger amounts of thiamine. The evidence for decreased cardiovascular efficiency is seen in the reduced performance in tests the limiting factor of which is the cardiovascular system.

67 Beck, C. S. An Intrapericardial Teratoma and a Tumor of the Heart. Both Removed Operatively, *Ann Surg* **116** 161, 1942.

68 Hussey, H. H., and Katz, S. Beriberi Heart Disease and Pulmonary Embolism. Report of Three Cases, *M. Ann. District of Columbia* **11** 247, 1942. Rascoff, H. Beriberi Heart in a Four Month Old Infant (with Four Year Follow-Up), *J. A. M. A.* **120** 1292 (Dec. 19) 1942. Garland, L. H., and McKenney, A. C. Roentgen Diagnosis of Vitamin Deficiency Cardiac Conditions, with Some Clinical Observations on Thiamin Deficiency. *Radiology* **38** 426, 1942. Moniz de Bettencourt, J. Circulatory Disorders Due to Avitaminosis B<sub>1</sub>. Review of Literature, *Amatus* **1** 247, 1942.

69 Johnson, R. E., Darling, R. C., Forbes, W. H., Brouha, L., Egana, E., and Graybiel, A. Effects of Diet Deficient in Part of Vitamin B Complex on Men Doing Manual Labor, *J. Nutrition* **24** 585, 1942.

**Oleoperitoneografia** Contribución al estudio radiológico del peritoneo By Carlos H Niseggi, Profesor Adjunto de Radiología de la Facultad de Medicina de Bs Aires, Jefe del Servicio Central de Radiología del Hospital Teodoro Alvarez, Miembro Fundador de la Sociedad Argentina de Radiología, Marcelo H Moreau, Medico Agregado del Servicio Central de Radiología del Hospital Teodoro Alvarez, Miembro Titular de la Sociedad Argentina de Radiología, and Joige E Moreau, Medico Interno del Instituto Municipal de Radiología y Fisioterapia, Buenos Aires Pp 195, with 153 illustrations Buenos Aires Libreria Y Editorial "El Ateneo," 1941

This relatively short monograph deals with the employment of oleoperitoneography in the study of the peritoneal cavity This procedure is of greatest value in the diagnosis of peritoneal fluid, as even the lesser degrees of ascites, which may have escaped clinical notice, may be detected in this manner Large abdominal cysts also may be recognized, as their roentgen appearance is characteristic during oleoperitoneography

The technic consists of intraperitoneal injection of 3 cc of iodized oil Roentgenograms are then made with the patient supine, prone and erect

The first seven chapters are devoted to a description of the peritoneal surfaces and the disposition and appearance of liquids and iodized oil in the peritoneal cavity in normal and in abnormal conditions Experimental work on animals is included

The remainder of the book consists of a series of observations in 40 clinical cases studied by the authors Each case is illustrated by one or more excellent reproductions of roentgenograms A short bibliography has been added

**Bronchiectasis** Pathogenesis, Pathology and Treatment By James R Liza, B S, M D, F A C P, Pathologist, City Hospital, Welfare Island, New York, and Milton B Rosenblatt, B S, M D, Associate Visiting Physician, City Hospital, Welfare Island, New York, Associate Attending Physician Montefiore Hospital Cloth Price, \$4 Size of page 6¼ by 9½ inches Pp 190 plus an index, with 40 illustrations and 4 tables New York Oxford University Press, 1943

This splendid monograph is the result of a painstaking study of 110 cases of bronchiectasis A review of the anatomy and the physiology of the bronchi precedes the chapter devoted to theories of the genesis of bronchiectasis Studies of the lesions encountered follow The pathogenesis, the clinical aspects and the treatment are then considered in the order given

The thesis elaborated throughout is that etiologically bronchiectasis is bacterial infection involving the bronchi and the adjacent parenchyma of the lung—it is not merely a dilatation of the bronchial tubes In the vast majority of these cases it was a sequela of bronchopneumonia in childhood but in many it was produced by other infections, including those resulting from bronchial occlusion

The book is printed on excellent paper, the illustrations are well selected and well reproduced There is an extensive bibliography The reviewer unhesitatingly recommends this work to all clinicians and students of medicine

**Primer of Allergy** By Warren T Vaughn Edition 2 Pp 176, with 26 illustrations and 5 charts Price, \$1.75 St Louis C V Mosby Company, 1943

One of the most serious problems of modern medicine is the question of education of the layman How and to what extent can and should this be done? The little book under consideration exemplifies one method snappy, slangy, epigrammatic discussion, illustrated by cartoons and slogans For example, chapter 1, entitled "Learn to Live with Your Allergy," is headed by a drawing of a peculiarly imbecilic-looking white elephant led by a ridiculous little figure and labeled "Man's White Elephant" This sort of thing goes on throughout the book and is doubtless supposed to drive home the various points in an impressive way The reviewer does not like this method He feels that serious matters should be dealt with in a dignified way, that authors should elevate their audience and not play down to it If these childish methods of instruction are really necessary, then there is indeed an intellectual decay among the citizens which demands decisive improvement of present educational methods

**A Text-Book of Pathology** By William Boyd Edition 4 Pp 1008, with 490 engravings and 29 colored plates Price \$10 Philadelphia Lea & Febiger, 1943

Dr Boyd's justly popular treatise appears now in a new edition Chapter 1, a brief philosophic discussion of the content of pathology, sets the stage, and the book then proceeds along conventional lines, dealing first with such general matters as degeneration, inflammation and tumors, and going on to the special diseases and organs The writer's style is

## Book Reviews

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**Mental Health in College** By Clement C Fry, M.D., with the collaboration of Edna C Rostow Pp 365 Price, \$2 New York The Commonwealth Fund, 1942

This work represents a survey of the case histories of some 1,257 university students who came under the observation of the authors in over a decade of experience at Yale University. The first third of the book is concerned with a definition of the problem a description of the materials of the study and a general discussion of "the problems of personality growth." The student environment at Yale University is then described (perhaps the most interesting part of the book), followed by a consideration of the psychiatric problems encountered by students of the various schools and departments in their personal, scholastic and social adjustments.

The book is informative and interesting as a general survey of the types of maladjustment seen among the students at an old, aristocratic university, where social factors are at least as important as the academic. It reveals much about Yale University as well as about the students. As a sociologic study the book has considerable value. As a contribution to psychiatric thought it is barren. Superficiality marks the discussion of individual case histories, none of which seems to have been extended to the point where the psychiatrist really understood his patient's inner psychologic problems. Perhaps little more was possible in view of the limited time available under the circumstances. Though the discussion of the importance of family relationships in the mental life of the student is good, the consideration of the sexual growth and behavior of the student only skims the surface. The important subject of treatment of patients with sexual problems is often dismissed with little more than such meaningless and vague statements as that "Treatment was directed at giving him a more informed attitude toward sex and increasing his insight into his whole personality." Sexual maladjustments are frequently attributed to "inadequate sexual information," and "a thorough education about sex" is often considered the correct treatment. Such statements may cover adequate management of these delicate problems, but they certainly do not tell the reader anything specific.

In general, the book is an interesting survey of the field, but it is of little value in helping to solve the problems it reveals.

**Sulfanilamide and Related Compounds in General Practice** Second edition By Wesley W Spink, M.D., F.A.C.P. Price, \$3.00 Pp 374 Chicago The Year Book Publishers, Inc., 1942

That the second edition of this book came out only a comparatively few months after the first edition speaks well for its authenticity as well as for its completeness. Very rapidly Spink's book on the sulfonamide compounds obtained popularity, and fortunately so, because this has enabled him to bring out a new edition in which he has been able to incorporate the rapidly evolving newer developments in therapy with these compounds that have taken place since the appearance of the first edition.

The second edition has undergone a complete revision, not only has new material been added, but some of the older material has been elaborated on and some has been deleted. This is, of course, in line with the advances that have taken place in therapy with sulfonamide drugs and the development of newer compounds by the chemists who have been working with these drugs.

The book has much to recommend it. It is reasonably short and concise but nevertheless sufficiently detailed to allow the practitioner to obtain all the information he may need for the treatment of certain diseases against which sulfonamide compounds have proved effective. For the investigator the very complete bibliography is sufficient to refer him to source material and to a more complete exposition than can be given in a relatively small book.

With practically all the details of treatment the reviewer is in accord. He is not in agreement, however, with a part of the chapter which has to do with prophylactic use of the sulfonamide compounds. He wishes that Spink had condemned rather than accepted the rather promiscuous use of these potent and sometimes dangerous drugs in the prevention of hypothetical complications of various conditions, which will probably never develop and which if they do can be minimized by one or another of the sulfonamide preparations.

## A NOTE CONCERNING THE LONG NEGLECT OF AUENBRUGGER'S "INVENTUM NOVUM"

JAMES B HERRICK, M D  
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In 1843 in a short introduction to Ungar's translation<sup>1</sup> of Auenbrugger's "Inventum novum" Josef Skoda in his brusque way declared that "to catalogue the reasons why Auenbrugger's discovery, which was so clearly set forth in his book was not noticed by his contemporaries would be a useless task" A study of his book, he said, showed that Auenbrugger with the fullest right might be looked on as the founder of modern diagnosis

Yet in spite of Skoda's pronouncement of a century ago the question has since that date been taken up more than once Two papers deserve especial notice, one by Noltenius, the other by Neuburger In 1908 Noltenius<sup>2</sup> published an exhaustive study of the problem of why the results of a scientific clinical investigation that had been carried on for seven years were gradually all but forgotten In 1922 Neuburger's<sup>3</sup> critical monograph appeared, which, based largely on the work of Noltenius would, as Sigerist<sup>4</sup> commented, seem to be the final word on the subject

Noltenius and Neuburger, disregarding Skoda's pronouncement, offered several explanations of why Auenbrugger's work was ignored by some, ridiculed by others, or assailed as not new but old, a mere revamping of Hippocrates The prevailing attitude of the medical mind of that day was philosophic and speculative, to employ manual help in diagnosis was banal and beneath the dignity of the high calling of the physician<sup>5</sup> Then there were weak points in Auenbrugger's method He sought for finer details than could be grasped by the beginner Unfortunately he gave the impression that by percussion *alone* a diagnosis could be reached Even his supporter Stoll (who in 1776 succeeded de Haen) acknowledged these failings

One must recognize also that there were some imperfections in the technic that made it difficult for practitioners who lacked Auenbrugger's skill, patience and experience to be as sure of their results as he was For example, he advised using one hand only Percussion was to be made not over the bare skin, the chest was to be covered with cloth, e g, the shirt Or the hand might be encased in a glove It can be readily understood how by such a procedure finer distinctions between tones might be missed, though they might be detected by the

1 Ungar, S Leopold Auenbrugger's Neue Erfindung, mittels des Anschlagens usw Uebersetzung mit Vorwort von J Skoda, Vienna, 1843 Later, a new edition appeared with a biographical sketch by Jadassohn, Berlin, 1908

2 Noltenius, B Zur Geschichte der Percussion von ihrer Bekanntgabe durch Auenbrugger (1761) bis zu ihrer Wiederbelebung durch Corvisart (1808), Arch f Gesch d Med 1 329-350 and 403-428, 1908

3 Neuburger, M Leopold Auenbrugger's Inventum Novum, Leipzig, Verlag von Josef Safar, 1922

4 Sigerist, H E Forbes' Translation of Auenbrugger, Baltimore, Johns Hopkins Press, 1936

5 Neuburger,<sup>3</sup> p 22

simple and lucid, to the reviewer the real difficulty is that the subject has outgrown the bounds of any one reasonable volume. Just as a random example, the "pathology" of thiamine is dealt with in a single paragraph of some dozen lines. However, if the student knows all that Dr. Boyd has to tell him in this compressed treatise, he will be doing well enough.

**Chemotherapy of Gonococcic Infection** By Russell D. Herrold. Price, not given. Pp 137. St. Louis: The C. V. Mosby Company, 1943.

The actual substance of this little monograph, namely the part dealing with chemotherapy of gonococcic infections, occupies a relatively small part of the book, the remainder is to some extent unessential. Even in the sections on chemotherapy matters of common knowledge are reported at considerable length. The description of the systemic complications of gonococcic infections does not seem very adequate, arthritis is dealt with on one page, there is no discussion of general gonococcic sepsis or of the interesting cutaneous lesions. The reviewer disagrees sharply with the statement (p. 76) that removal of so-called chronic focal infections (teeth, tonsils, etc.) serves any particular purpose in gonococcic infections.

**The March of Medicine: The New York Academy of Medical Lectures to the Laity, No. 7** Price, \$2.50. Pp 217, with 11 figures. New York: Columbia University Press, 1943.

The names of the writers, J. A. Miller, Tracy Putnam, A. A. Brill, Gesell, Jolliffe and Carlson, are enough to guarantee the high quality of the lectures. The value of medical presentations to the laity is always hard to assess, lecture audiences are notably of mixed intelligence. It seems worth while, therefore, that these discussions should appear in print, so that persons really interested can consider them at leisure. Tuberculosis, psychology and psychiatry, and nutrition make up the chief topics.

**Renal Lithiasis** By Charles C. Higgins, M.D. Price, \$3.00. Pp 140, with 18 figures. Springfield, Ill.: Charles C. Thomas, Publisher, 1943.

This little book, handsomely printed and illustrated, is an elaboration of the author's Beaumont Lecture on renal lithiasis. A considerable portion of the text is devoted to reports of the animal experiments on which the author bases his view that vitamin A deficiency plays a major role in the development of certain types of renal stone. A section on operative treatment comes next, and finally diet lists of foods high in acid ash and vitamins. There are a bibliography and an index.

**The Neuromuscular Maturation of the Human Infant** By Murtle B. McGraw. Pp 140, with 28 figures. Price, \$2. New York: Columbia University Press, 1943.

This scholarly little monograph deals in a highly technical manner with the details of development of neuromotor activities in the newborn. All the various reflexes, such as rolling and turning, receive meticulous consideration, and the whole subject is developed against a background of the general problem of behavior as well as neuroanatomy. This volume will surely have to be consulted by special workers in the field.

**Flying Men and Medicine** By E. Osmun Barr. Price, \$2.50. Pp 270, with 10 drawings. New York and London: Funk & Wagnalls Company, 1943.

"Here is the story of aviation medicine told in simple English." This statement of the publisher, taken from the jacket, summarizes very well the contents of the book. The writing is excellent, and the material is comprehensive and soundly dealt with. The story is told in a vivid, but not sensational, manner. The layman interested in aviation should find it interesting reading. There is an index.

diseases of the chest, nor in any way to belittle the importance to medicine of his remarkable volume, "the little book so small, so terse, so wonderful," as Weir Mitchell<sup>7</sup> termed it. It was largely because of the stimulus given by the "Inventum novum" that the work of Corvisart, who revived Auenbrugger (1808) and generously gave him full credit for his discovery, as well as the work of Laennec, of Skoda himself and of others made Auenbrugger's place in the hall of fame forever secure.

The long neglect of Auenbrugger is not a unique occurrence. While the worth of some epoch-making medical discoveries has been promptly recognized, delay in acknowledging the merit of others has led to tedious, perhaps ill tempered discussion and to resentful reaction on the part of the discoverer and his friends. Some, like the sensitive Semmelweiss, after pleading in vain, after brooding until worn out, have finally broken down. Had Semmelweiss flared up with a violent outburst of angry invective, the result might have been less tragic. When Scotch reviewers unjustly attack it may be better to fight back as did Byron than to wilt as did the hypersensitive Keats.

Some, however, did not break down. Vesalius bitterly resented the criticism of his contemporaries. In a fit of anger he burned his books and manuscripts, gave up teaching and, shaking the dust of Padua from his feet, left that city to become the court physician of the Emperor Charles V. Nor did the peppery Harvey suffer in silence. In 1649, in his second disquisition to Riolan of Paris, he referred to contemporary critics of his "De motu" as detractors and mummers who were unworthy of an answer. "Let them consume on their own ill-nature. They will scarcely find many well-disposed readers, I imagine, nor does God give that which is most excellent, and chiefly to be desired—wisdom—to the wicked. Let them go on railing, I say, until they are weary, if not ashamed."<sup>8</sup>

Yet Auenbrugger's action was strangely different from that of Semmelweiss, Vesalius and Harvey. He did not wait to be attacked, he *anticipated* such action. He expressed beforehand the utmost contempt for those who, he said, *would* attack him, declared he would not deign to answer them. In general he seems to have kept this vow.

That the forty years' neglect of Auenbrugger was in large measure due to the causes so thoroughly considered by Noltenius and Neuburger is clear. Yet, in addition, commentators have generally charged that much of the onus for this unfortunate and tragic occurrence must be borne by the two leaders of Viennese medicine of that time, van Swieten and de Haen. Had these two men been friendly, had they publicly endorsed Auenbrugger, all would have been well, one is told. Instead, they preserved an "icy silence." They ignored the industrious young scientist, though they were familiar with his work, for it was carried on largely in their wards.

Auenbrugger has been all but canonized by his admirers. The purpose of this paper is to offer the rather heterodox suggestion—I dare not use a stronger term, like "claim"—that the fault may have lain, much more than is generally recognized, in Auenbrugger himself, in his peculiar personality. Perhaps, after all, he was human, with the frailties of ordinary human beings.

For some reason he did not always get along well with his fellow workers in the wards. Is it not possible that while working in the Spanish Hospital, using many patients that had been loaned him through the courtesy of de Haen and van Swieten, his attitude toward his associates and his superiors gave offense?

<sup>7</sup> Mitchell, S. W. Early History of Instrumental Precision in Medicine, New Haven, Tuttle, Morehouse & Taylor, 1892, p. 24.

<sup>8</sup> Powers, D'A. William Harvey, London, T. F. Unwin, 1897, p. 226.

musical ear of the discoverer, and the sense of resistance would be lost. Then, especially in the latter half of his book, there was vagueness, and even some error, in the presentation of his subject. All of these facts tended toward bewilderment rather than clarification in the mind of the reader.

That many failed to read the book at all or read it carelessly, confusing Auenbrugger's method with the Hippocratic succussion sound, is clearly brought out by Noltenius. In large measure, as Dock<sup>6</sup> emphasized, this was due to indolence, they were too lazy to read carefully, and they did not bother to translate accurately. And Neuburger was probably right in his caustic statement that the number of



*Leopoldus Auenbrugger medicus viennensis*

LEOPOLD AUENBRUGGER, 1722-1809

Fig. 1—Leopold Auenbrugger (from Sigerist, H. E. *The Great Doctors*, New York, W. W. Norton & Company, Inc., 1933, facing p. 240)

those who were not able to hear when they percussed was decidedly smaller than the number who did not wish to hear. They were against the revolutionary ideas of the young upstart.

Finally, Auenbrugger's Latin was not always clear, a point brought out by Ungar,<sup>1</sup> which will be taken up later.

In offering my views there is no intent to dispute the claim that Auenbrugger was a pioneer in modern diagnosis, at least as it concerns physical diagnosis of

<sup>6</sup> Dock, G. Leopold Auenbrugger and the History of Percussion, *Michigan Alumnus*, November 1898.

Most commentators have referred to Auenbrugger as a modest, unassuming man who was a martyr to the ignorance and the ill natured opposition of his contemporaries de Haen and van Swieten. Ungar in his preface to his translation of the "Inventum novum," said that in "1761 the book appeared timidly and modestly" (*zaghaft und bescheiden*). But is this the spirit shown in Auenbrugger's preface? Was he not a little toplofty, "biggity" as Uncle Remus would say, when he declared that after seven years of study he *knew* (italics mine) that his results were correct? Readers, he said, would of course be influenced as they had been in the case of other investigators, by envy, malice, hatred, detraction and calumny. He expected to be vilified. But he did not propose to waste any effort in the future to reply to criticism or to advance further proof. He seems to have been saying "Take it or not, I am indifferent as to what you do. I admit that much remains to be discovered, but—let others do the work, I'm through." This failure of Auenbrugger to follow up the rich lead he had discovered was aptly referred to by Dock<sup>9</sup> as strange and unexplained.

Now could the two leaders of the Vienna school be expected to bestow an approving pat on the back of this young man of 39 years who assumed such a lofty, almost defiant, pose? Was it not asking too much of them? The tempestuous 57 year old de Haen, true to form, opposed the innovation because, forsooth, as Neuburger<sup>10</sup> has said, he was not its author. Van Swieten, then 61, better poised and peace loving, though he had been referred to by Auenbrugger in complimentary terms as the illustrious Baron van Swieten, quietly ignored the remarks of his pupil that, to say the least, were tactless. Possibly van Swieten may have said to his colleague de Haen, as he once wrote him on another occasion and on another topic, "What's the sense of all this row? Quiet down. I never count a fight."<sup>11</sup> That they did ignore him is shown by the fact, vouched for by Noltenius and confirmed by Clar,<sup>12</sup> that in the voluminous writings of these two men—de Haen in 1769 had fifteen volumes to his credit—not one reference to Auenbrugger and his percussion is to be found. Ungar said van Swieten may perhaps have given him the *slightest* notice, thus damning him with faint praise. Noltenius,<sup>13</sup> however, said that van Swieten's "Commentaries on Boerhaave's Aphorisms," though discussing hydrops and empyema of the chest, made no mention of percussion. May not Auenbrugger's attitude explain in part the indifferent or unfriendly reception given by these men to his book?

As an extenuating circumstance that may help explain the resentful behavior of Auenbrugger one may surmise, as did Noltenius, that Auenbrugger had been subjected to criticism and ridicule by skeptical physicians who saw him at work day after day in the wards, going through a performance that to them seemed nonsensical. After seven long years of such unpleasant treatment it can be understood how all this "got under his skin," how he became exasperated, irritable, rebellious. One may surmise also that Auenbrugger was unaware of the state of his own mind at the time he wrote. He may have harbored in his subcon-

9 Dock, G. Roziere de la Chassagne, and the Early History of Percussion of the Thorax, Ann M Hist 7 438-450, 1935

10 Neuburger,<sup>3</sup> p 26

11 See Ebstein, E. *Ärzte-Briefe* aus vier Jahrhunderten, Berlin, Julius Springer, 1920, pp 18-24. Strangely, too, in this same letter, written Sept 10, 1761, he also said "I am not ashamed to learn from a young physician." Though there is no warrant for assuming that van Swieten had Auenbrugger in mind when he wrote this, it is a striking coincidence that the preface to Auenbrugger's book was dated only a few months before this time, Dec 31, 1760. The volume itself appeared early in 1761.

12 Clar. Leopold Auenbrugger, der Erfinder der Percussion des Brustkorbes, geb zu Graz 1723, gest zu Wien 1809, und sein Inventum novum, Graz, Leuschner u Lubensky, 1867

13 Noltenius,<sup>2</sup> 338





*g: Van Swieten.*

GERHARD VAN SWIETEN, 1700-1772



*A de Haen*

ANTON DE HAEN, 1704-1776

Fig 2—Gerhard van Swieten and Anton de Haen (from Sigerist, facing p 209)

sting concealed here? Or may, possibly, de Haen and van Swieten, those experts in prodigal wordiness, have felt that there was a covert reference to themselves?<sup>15</sup>

The period 1761 to 1776, the year when de Haen died, the period in which the method of percussion was treated partly by dead silence, partly by scorn, was not an entirely happy one for Auenbrugger, as quotations from his writings have shown. Yet he was by no means entirely unhappy. He was busy with practice and was called in consultation by physicians and surgeons, especially in cases of disease of the chest. He was popular as a practitioner, noted for his kindness to the poor, happy in his home life and in his love of music, a welcome guest in social circles. "A grave, contented, music-loving German" Weir Mitchell<sup>16</sup> called him. Honors came to him later. In 1784 he was elevated by the Emperor Joseph to the nobility as "Edler von Auenbrugger." While his last years were made sorrowful by impaired eyesight and by the loss of his wife, in 1807, it surely must have cheered the heart of the old man to know that, owing to Corvisart, his work was at last accorded the world praise that was long overdue. He died May 18, 1809, in his eighty-seventh year.

#### AUENBRUGGER'S LATIN

The terseness of Auenbrugger's Latin and its predominant clarity have justly excited favorable comment. Yet, in places, and in a measure because of this terseness, one has difficulty in getting the exact meaning. Ungar<sup>1</sup> referred to his Latin as "etwas dunkel." "The peculiarity of the author's style, the frequent ambiguity of expression, the apparent contradiction in places of statements found elsewhere, the incompleteness of the terminology have made the interpretation difficult."

I omit as not germane to the question discussed in this paper all consideration of the critical study made by Ungar of various portions of the main body of the text of the "Inventum novum." Attention is directed to the preface and especially to the ninth sentence, which is also the ninth paragraph. That the meaning of this paragraph is not clear is shown by the fact that it has been translated by different commentators in several ways. It reads as follows:

Et haec erat ratio, cur cum signis quieverim, atque etiam in his, ad inevitabilem causarum quarundam enumerationem, quae ad illustrandas observationes meas conferre poterant, confugerim ad commentaria Illustrissimi L. Baronis van Swieten, quoniam in his, quid quid ab observatore Homine desiderari unquam potest, absolutum invenitur.

The English translation (Forbes) reads: "Owing to this acknowledged imperfection, it will be seen, that, in my difficulties, I have had recourse to the Commentaries," etc. In the French (Corvisart) it is interpreted to mean: "This is the reason why when I felt the lack of signs," etc. ("lorsque je manquai de signes"). Ungar said Corvisart's translation of "et haec ratio" is forced and not in agreement with the preceding sentence. The translation of "quiescere" is contrary to "every Latinity," he declared. The German translation, as it seems to me, comes nearer to the meaning, it interprets "quiescere" as "to be satisfied with" ("es bei bewenden lassen").

<sup>15</sup> I may add that much later, in 1867, Clar of Graz, who though he defended Auenbrugger yet made critical, not always laudatory, comments on his work, was guilty of tremendous long-windedness, as witness one sentence of about 550 words covering a page and a half. The only other writer whom I have run across who compares with him in this respect is Friedrich Kreysig (Herrick, J. B. A Short History of Cardiology, Springfield, Ill., Charles C. Thomas, Publisher, 1942, p. 81).

<sup>16</sup> Mitchell,<sup>7</sup> p. 24.

scious stratum a tenseness that was close to the breaking point. When the book had been published, when this tenseness was relieved, when he was sadly disillusioned as to hoped-for praise by van Swieten, he may have sorrowfully realized what he had done and how he had given offense.

Early in 1762 he manifested resentment when he referred to the jealousy and misunderstanding of colleagues. In the preface to a book dealing with the treatment of mania in men, "Experimentum nascentis de remedio specifico," he said that "the history of my last patient is incomplete because today—January 14, 1762—my subordinate in rank who later became my successor, induced by clandestine motives to my surprise and without telling me about it discharged the patient from the hospital." Also, in the foreword to the book he unquestionably referred to himself when he quoted "ratus enim propheta in patria." Further, in 1776 in a letter to Haller<sup>14</sup> which accompanied a gift copy of the book "Experimentum nascentis" he apologized for certain imperfections, and said

*Illustrissimo*  
*Magnifico ac Celeberrimo Viro*  
*Sommo Alberto de Haller. etc. etc.*  
*S: S.*  
*Leopoldus Auenbrugger medicus viennensis*

*Mitto Tibi, Vir celeberrime, librum, cui Titulus*  
*est, Experimentum nascentis, de Remedio specifico,*  
*sub Syno specifico, in Mania Virorum, qui obser-*  
*vationum mearum Ratus est, doleo imperfectus,*  
*non quidem mea culpa, sed — — — !*

Fig 3—Facsimile of the first paragraph of Auenbrugger's letter to Haller (from Neuburger,<sup>14</sup> facing p 24)

he trusted they might be overlooked, for it was not his fault that they were there. "Non quidem mea culpa est, sed . . . !" One can only wonder what is meant by the "sed . . . !"

It is not easy for one today to interpret correctly what may have been the true intent of something written nearly two centuries ago. Correct interpretation demands a retrojection of the commentator into the past so that so far as possible he realizes conditions as they were at that time. Contemporaries are to be judged by the yardstick of their time and not by that of today, as Neuburger put it. It is because this cannot be satisfactorily done that it may be unfair even to hint that when in his preface to the "Inventum novum" Auenbrugger said, "I prefer to express myself in a few words," in his own mind he underscored the word "I." Could it be that there was—perhaps unintentionally—a satirical

<sup>14</sup> Neuburger's Monograph<sup>3</sup> (facing page 24) has a photostatic copy of the autograph letter, as well as one of a letter of sympathy to Haller, whose son had died in 1778.

# SCLERODERMA HEART DISEASE

WITH A CONSIDERATION OF CERTAIN OTHER VISCERAL MANIFESTATIONS  
OF SCLERODERMA

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AND

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It is the purpose of this paper to call attention to the involvement of organs other than the skin in the course of scleroderma and to discuss particularly the clinical and the pathologic changes resulting from myocardial lesions associated with this condition

The physician frequently encounters patients with heart disease which does not fit into any of the various categories usually listed in textbooks of medicine<sup>1</sup> Unless particular attention is paid to the establishment of the etiologic factors underlying the condition one is likely to miss the significance of certain rare forms of generalized disease which may lead to myocardial failure It is easier to conclude that a given patient suffers from an unusual manifestation of arteriosclerotic, hypertensive, rheumatic, syphilitic or congenital heart disease than it is to establish the association of myocardial changes with some less familiar condition which may affect the heart One of these less familiar conditions is scleroderma

Because of the forcing of certain cases into the better recognized forms of heart disease the progress of knowledge regarding etiologic classification has been handicapped Accurate etiologic classification is of practical, as well as of theoretic, importance, because many of the rarer forms of heart disease are amenable to specific therapy Although the incidence of any one of these less common forms of heart disease is not great, the group as a whole comprises an appreciable percentage of the instances of cardiac disease encountered in medical practice The observation that generalized scleroderma was one of the "not well recognized" causes of heart disease led to the present study

The causation of the generalized form of scleroderma is not known<sup>2</sup> It occurs in females about twice as often as in males and most frequently in persons in the fourth and the fifth decade, but it can occur at any period from infancy to old age The course is extremely variable, the onset may be insidious with many years required for its full development, or the disease may appear and progress

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† This paper represents an expansion of material collected by Dr Weiss before his death on Jan 30, 1942 Dr Weiss presented this material in part at a meeting of the New England Heart Association in Boston on Dec 15, 1941

1 Weiss, S Diseases of the Heart and the Aorta Which Are Not Well Recognized, M Clin North America **23** 1323 (Sept) 1939

2 Burch, G E Scleroderma Etiology and Abnormal Physiology New Orleans M & S J **92** 12 (July) 1939

In my perplexity over the proper translation of this sentence I appealed for help to my friend Payson S. Wild, of Chicago, well known as an expert classical scholar. I am grateful to him for his opinion in the matter. He believes that "quieverim," as well as "confugeim" depends not on "cum" but on "cur." "Cum" is a preposition followed by "signis", it really goes with, or is a part of, "quieverim." Facciolati and Forcellini, in their "Totius Latinitatis Lexicon," have cited examples from classical Latin in which—*per synecdochem*—"quiescere" is used as the equivalent of "omittere or desinere," translated in English "to give over," "to leave off." Auenbrugger seems to have followed a German usage—much like the use of *aufhören*. He meant to say he "broke off with" the signs, stopped considering or experimenting with these signs. The sentence may then be translated "And this was the reason why I stopped experimenting with these signs, and why also, as an aid in the necessary listing of certain causes that could assist in making clear my observations, I had recourse to commentaries of the most illustrious Baïon van Swieten, since in these whatever is needed by the observant individual is sure to be found."

He continued in the next paragraph "I thus avoided the need of prolix writing and also laid a most secure foundation on which the rudiments of my discovery would more creditably rest."

#### SUMMARY

That the "Inventum novum" was all but forgotten until revived by Corvisart in 1809 was largely due, as shown by others, to several factors. Auenbrugger gave the wrong impression, viz., that by percussion alone a diagnosis could be made. His technic was not perfect—e.g., he used one hand only and that often covered by a glove—so that less skilled physicians failed to get the hoped-for results. Many who read his book carelessly, if at all, thought he was merely revamping the old Hippocratic sound. The meaning of his Latin was at times obscure. Especially, a large part of the blame has been attributed to the "icy silence" of his seniors, de Haen and van Swieten, in whose wards he worked.

In this note the question is raised whether Auenbrugger's own personality may not have had much to do with alienating de Haen and van Swieten. There is presented evidence that he had difficulty in getting along with other workers in the wards. In his preface his words reveal a toplofty or defiant attitude, he knew he was right, though much remained to be done in perfecting the method, he was through, others must do it, he expected to be vilified as other contributors to science had been but he would not deign to answer criticism of any kind. All this may have given offense to these Viennese leaders. That he was keenly disappointed by the action of his chief, van Swieten, is clear. That he was tensely nervous and irritable is highly probable. Even long after 1761 his resentment is shown by excerpts from letters. A critical study of a paragraph from his preface is added as an attempt to clear some of the obscurity of his Latin.

In offering this rather heterodox explanation I wish to declare my admiration for Auenbrugger's talent as an original investigator as well as for the content and terse Euclidean style of the "Inventum novum." His place in the hall of fame is forever secure.

For about one year prior to admission the patient experienced gradually increasing dyspnea, which became quite severe during the two or three months before admission. Associated with this she had moderate swelling of the ankles, and for five or six weeks her face was swollen on arising in the morning. In the month prior to admission she became orthopneic and spent several nights sitting up in a chair. She also had a dry cough and occasionally woke up at night with a severe coughing spell and dyspnea. At such times she would frequently cough up white frothy sputum.

A year or so before admission she began having "heartburn" and would often have a feeling of substernal fullness soon after eating. On rare occasions this was accompanied by vomiting. There were no other gastrointestinal symptoms. A review of each system failed to reveal any other complaints.

*Physical Examination*—On admission to the hospital the patient was well developed but poorly nourished. The skin of the entire body had a "tanned" appearance and was tight, shiny and inelastic. The changes were most marked about the face, arms and hands. There were several small areas of nonpigmented skin. There was moderate thinning of the hair. The face was expressionless, the mouth was small and could be opened to a limited extent only. The retinal vessels were not abnormal. The voice was rather hoarse. The

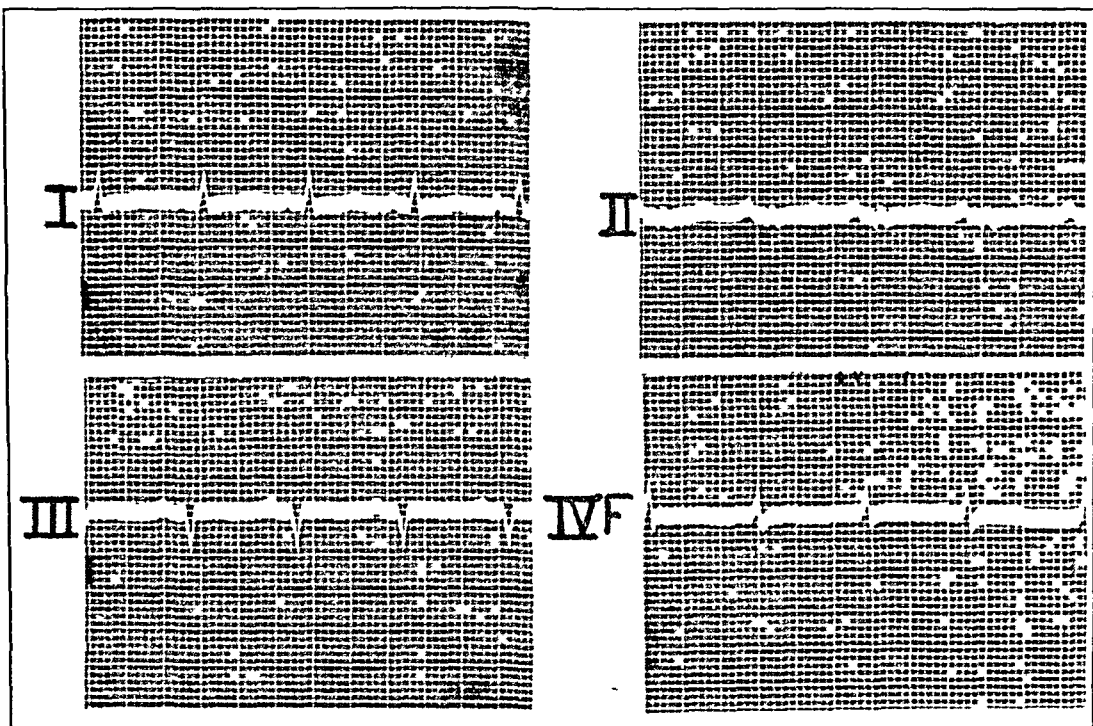


Fig 1 (case 1)—An electrocardiogram

veins of the neck were distended, and the neck was slightly stiff. Examination of the lungs revealed slight dullness and moist rales at both bases posteriorly. The heart was moderately enlarged to the left. The rate was rapid and regular except for an occasional premature beat. The sounds were of good quality, and there was a slight apical systolic murmur with a proto-diastolic gallop sound. The pulmonic and the aortic second sounds were of equal intensity. The arterial pressure was 140 systolic and 100 diastolic. The abdomen was rather full and tense, but examination failed to reveal definite evidence of fluid. The edge of the liver was not felt, but there was dullness and tenderness in the right upper quadrant of the abdomen. The spleen could be felt to descend on deep inspiration. There was moderate edema of the sacral region and the ankles.

*Laboratory Examination*—The hemoglobin content of the blood and the red and the white cell count were normal. The specific gravity of routine specimens of urine ranged as high as 1.022. All samples contained albumin (3 plus), and two contained occasional red and white cells. The total serum protein was 6.7 Gm per hundred cubic centimeters, with 3.3 Gm of albumin and 3.4 Gm of globulin. The serum per hundred cubic centimeters contained 152 mg of cholesterol, 10.2 mg of calcium and 4.0 mg of phosphorus. There was 48 per cent excretion of phenolsulphonphthalein in two hours. Vital capacity was 1,100 cc. The circulation time

to a fatal termination in a few weeks.<sup>3</sup> The early stages of the disease may be characterized by the presence of slight edema, induration and inflammatory changes in the skin, to be followed later by the more characteristic, tight, "hide-bound" skin, usually deeply pigmented, but with occasional areas of pigment loss. The skin may vary in color from ivory to dark bronze, like that seen in hypoadrenalism with pigmentation. The skin of the extremities and the face is commonly involved, but that of the entire body is also frequently affected. In many cases Raynaud's syndrome occurs either before, simultaneously with or after the onset of scleroderma. There is frequently a history of symptoms referable to joints, and a diagnosis of rheumatoid arthritis may be made before the scleroderma becomes obvious. Atrophy of the skeletal muscles often occurs. This happens not only under the sclerodermatous skin but distant from it, probably because of disuse. There may be slight fever, malaise and constitutional symptoms.

Various laboratory procedures have not given consistently abnormal results. There may be slight anemia. The basal metabolic rate usually is within normal limits but may be moderately elevated or, more frequently, depressed. Roentgen examination of the involved parts may show decalcification of bone or even loss of bony substance in the terminal phalanges, and at times there may be calcified areas in the skin.

When first described, scleroderma was regarded as a disease restricted to the skin, but later writers on the subject have described manifestations in other organs. It is now well known that the disease may affect the lungs, the endocrine glands and the gastrointestinal tract.<sup>4</sup> Although pathologic changes in the heart have been reported in a few cases,<sup>5</sup> cardiac symptoms during the course of scleroderma have rarely been described. The following cases are reported because they all have aspects which suggest the presence of heart disease of an unusual type in patients with generalized scleroderma. Other instances of generalized scleroderma have been encountered in which there has been suggestive evidence of myocardial involvement. Because our data on the latter cases are incomplete, they are not recorded here.

#### REPORT OF CASES

CASE 1—M. W., a housewife aged 27, was admitted to Peter Bent Brigham Hospital in 1940.

*History*—Six years before admission she noted that her hands were frequently cold and clammy, and in August 1934 her hands turned a "waxy white" while she was swimming. At this time she also had mild aching in both wrists. The symptoms became more frequent and severe, and in October 1935 right and left cervicothoracic sympathectomies were performed. Although there was temporary improvement, the symptoms returned and were accompanied later by pain and cyanosis of the fingers. Three years before admission persistent deformity of the hands first developed, with flexion contractures and occasional swelling. About one and a half years before entry she noted pigmentation of her hands, which she thought at first to be just "tan." At the same time a few areas of depigmentation appeared in the skin. The skin of her face, hands and feet became tight and shiny, later the skin of the entire body became involved. From time to time small ulcerated areas would appear on her finger tips and over bony prominences.

3 MacCallum, W. G. Acute Diffuse Scleroderma, *Tr. A. Am. Physicians* **41** 190, 1926.

4 (a) Matsui, S. Ueber die Pathologie und Pathogenese von Scleroderma universalis, *Mitt. a. d. med. Fak. d. k. Univ. zu Tokyo* **31** 55, 1924. (b) Linenthal, H., and Talkov, R. Pulmonary Fibrosis in Raynaud's Disease, *New England J. Med.* **224** 682 (April 17) 1941. (c) Ochsner, A., and DeBakey, M. Scleroderma. Surgical Considerations, *New Orleans M. & S. J.* **92** 24 (July) 1939.

5 (a) Brock, W. G. Dermatomyositis and Diffuse Scleroderma, *Arch. Dermat. & Syph.* **30** 227 (Aug.) 1934. (b) Matsui, <sup>4a</sup>

of the thyroid, bilateral degeneration of the crura of diaphragm and of the second and the third intercostal muscle

*Autopsy*.—The skin in all regions was smooth, thick and leathery in texture. Only with great difficulty could the skin be lifted from the underlying tissues, and no wrinkling resulted from this procedure. Over the lower portions of the abdomen and about the neck, wrists and lower parts of the forearms the skin was dark brown. This was in contrast to areas which were pure white, distributed in patches over the abdomen and in longitudinal linear streaks in the heavily pigmented regions of the neck and wrists. The rest of the skin was white, without areas of deep pigmentation. Because of the induration of the skin, the fingers were fixed in a position of flexion. There were small ulcerated lesions on the second and the fourth finger of the right hand, on the right knee and on both internal malleoli. The distribution of body hair was normal. On external examination subcutaneous edema was demonstrated in both legs, over the sacrum and in the labia majora.

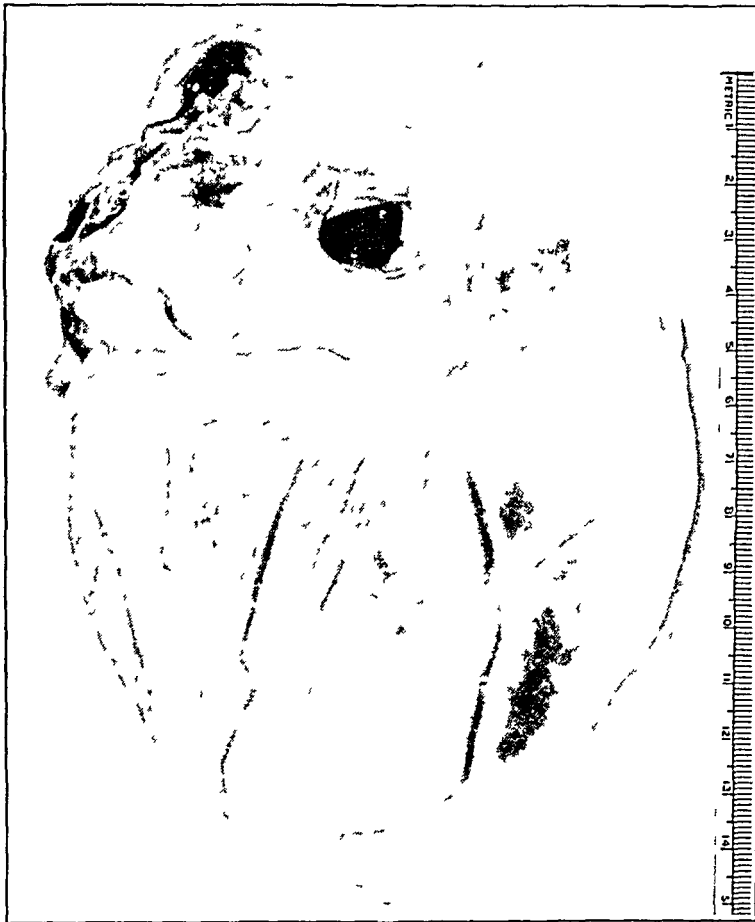


Fig 3 (case 1).—The posterior aspect of the heart. The heart is globular. There are numerous scars in the walls of both ventricles, for the most part linear in distribution.

In making the primary incision it was noted that there was marked edema of all subcutaneous tissues, the edema being apparent to external examination only where maximal because of the induration of the skin. There was no subcutaneous fat. The second and third intercostal muscle on either side was grayish pink and reduced in size. Other voluntary muscles were pale but normal in contour.

The peritoneal cavity contained 600 cc of clear, yellow fluid. The crura of the diaphragm on both sides were slightly thinner and considerably paler than the central portions.

The left pleural cavity contained 750 cc of yellow fluid and the right one 900 cc. There were a few easily broken adhesions about the apex of each lung. The pleural surfaces were smooth, moist and glistening. Examination of the mediastinum showed nothing abnormal.

The parietal pericardium was markedly edematous and gelatinous in appearance. Three hundred and forty cubic centimeters of yellow fluid was present in the pericardial cavity. The serous surfaces were free from exudate.



with sodium cyanide (arm to carotid sinus) was forty-two seconds. The venous pressure in the antecubital vein was 250 mm of water, the normal range by the method used being 50 to 150 mm of water. Pericardial fluid (obtained at postmortem examination) was clear yellow, with a specific gravity of 1.017 and a total protein content of 3.7 Gm per hundred cubic centimeters. Electrocardiograms showed low electromotive force, slight left axis deviation, low T waves and premature auricular and ventricular beats (fig 1). Roentgen examination revealed marked cardiac enlargement, both to the right and to the left (fig 2). The heart was triangular in shape and had a wide base. The amplitude of the beat was diminished. The findings suggested the diagnosis of a pericardial effusion. There were moderate pulmonary congestion and fluid in both pleural cavities. Roentgenograms of the hands and wrists showed

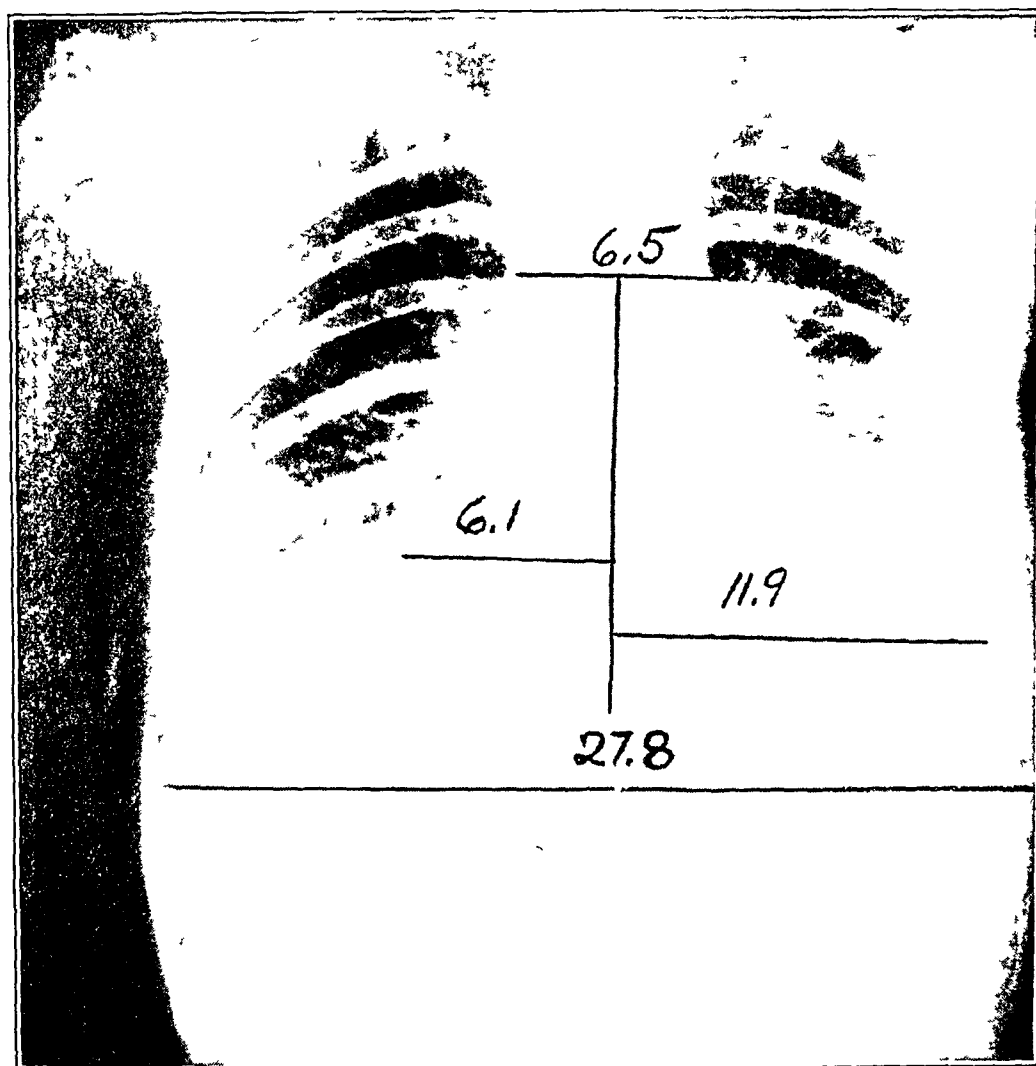


Fig 2 (case 1)—A roentgenogram of the chest. The heart is greatly enlarged. It is triangular, with a broad base.

definite atrophic changes, with partial loss of the terminal phalanges, more marked on the right hand.

*Course of Illness*—The patient's temperature remained normal throughout her stay in the hospital. The pulse rate ranged between 80 and 110 beats per minute. She continued to have respiratory difficulty despite therapy with digitalis, ammonium chloride and mercurpurin. On the eleventh day in the hospital, while sitting on the edge of her bed eating lunch, she suddenly fell back on the bed, rapidly became unconscious and cyanotic, gasped a few times and died.

*Anatomic Diagnoses*—The anatomic diagnoses included scleroderma, myocardial cicatrization, hydropericardium (340 cc), bilateral hydrothorax, ascites, generalized edema, chronic passive congestion of the liver, splenomegaly (weight of spleen, 280 Gm), atrophy

ing to the points of origin of the posterior papillary muscles. This area was puckered, somewhat concave and firm in texture. The cut surface of the myocardium was paler than usual, with irregular firm white streaks among the bundles of muscle. All valves were normal. The coronary arteries were not thickened or occluded. Their intimal surfaces were entirely free from atheromatous plaques.

The right lung weighed 270 Gm, the left one, 230 Gm. There was normal crepitanity in all lobes. Surfaces made by cutting were pale pink, a small amount of pink fluid was expressed by pressure. The hilar lymph nodes were normal.

The spleen weighed 280 Gm. It was firm in consistency, and the capsule was not wrinkled. The color of the cut surface was deep red, traversed by firm white lines. Thin sections held their shape perfectly.

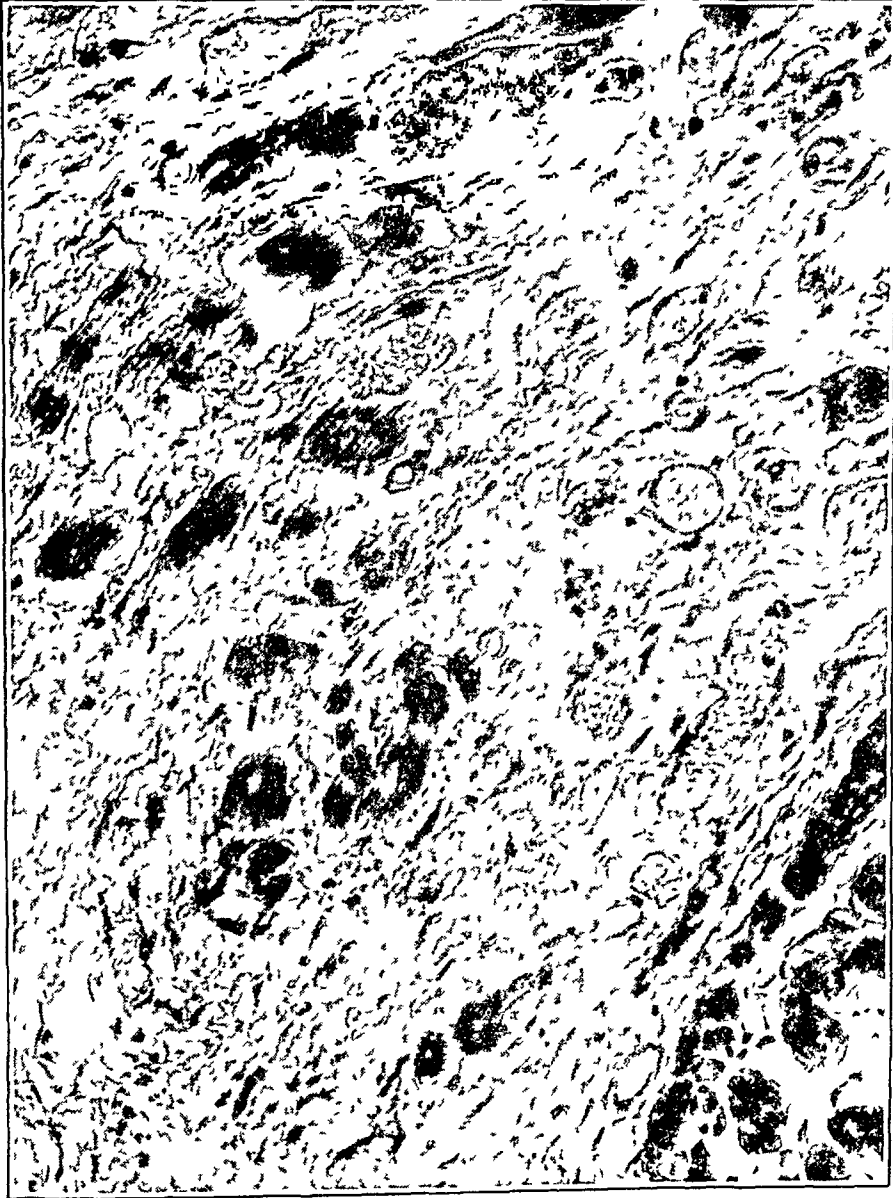


Fig 5 (case 1)—An area of scarring within the myocardium. The scar is composed of collagenous tissue rich in fibroblasts and in capillaries. A few muscle fibers remain well up within the lesion. Eosin-methylene blue stain,  $\times 300$ .

The liver weighed 1,380 Gm. The capsule was not thickened. The organ was firm in consistency and deep red in color. Externally, as well as in cross sections, there was conspicuous lobular mottling, consisting of deep purple central zones surrounded by pale yellow hepatic parenchyma.

The thyroid weighed 22 Gm. It was uniformly firm in consistency. Little colloid could be seen in the deep red, meaty surface exposed by cutting.

The aorta was elastic and free from atheroma.

The heart weighed 300 Gm and was globular in shape. A moderate amount of pale epicardial fat was distributed chiefly along the course of the coronary vessels. Over the anterior surface of the left ventricle, just to the left of the interventricular septum, there were numerous linear white areas involving both the epicardium and the superficial portions of the myo-

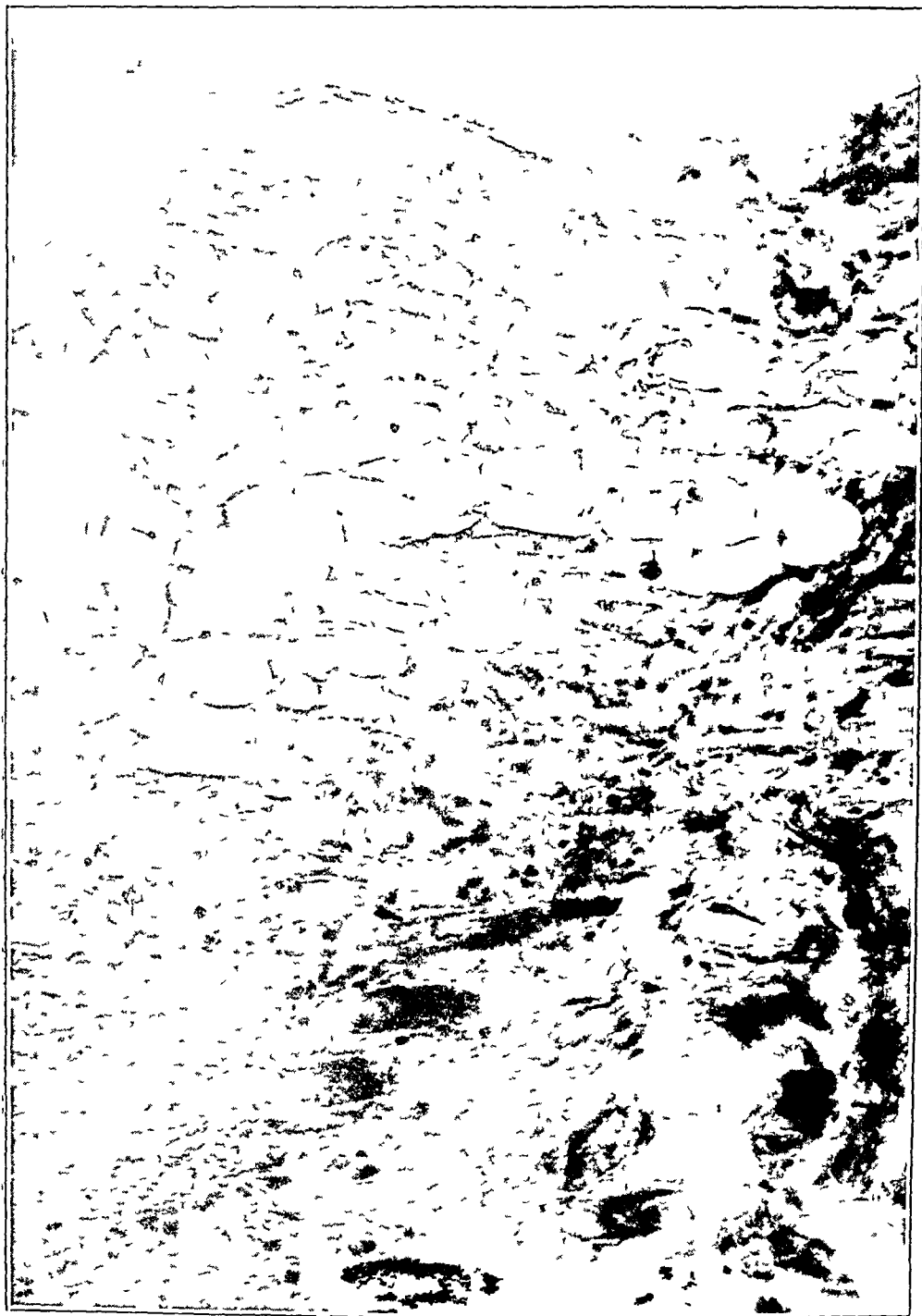


Fig 4 (case 1)—A scar in the superficial part of the myocardium with extension into the subepicardial fat. The connective tissue beneath the mesothelial layer is increased in amount. Eosin-methylene blue stain,  $\times 300$ .

cardium. These areas measured 1 to 2 cm in length. They were somewhat firmer than the intervening tissue. On the posterior aspect of the heart (fig 3) similar white areas were present in even greater numbers. There was one white region 2.5 cm in diameter correspond-

logenous tissue rather than a primary process to which the proliferation of connective tissue might have been a response. No areas of recent infarction were encountered.

In sections which did not contain focal areas of fibrosis, there was a diffuse broadening of the bands of the myocardial connective tissue. The fibrous tissue was edematous, delicately fibrillar and rather cellular in character. Capillaries were abundant and conspicuously engorged. The myocardial fibers in these areas were normal in appearance.

The endocardium was normal in thickness in many areas. Elsewhere, however, it was greatly thickened by an increase of fibrous tissue, which blended with the connective tissue of the underlying myocardium.

The epicardial surfaces showed no evidence of inflammatory change. In several places, however, there were focal areas of lymphocytic infiltration in the epicardial fat. From place

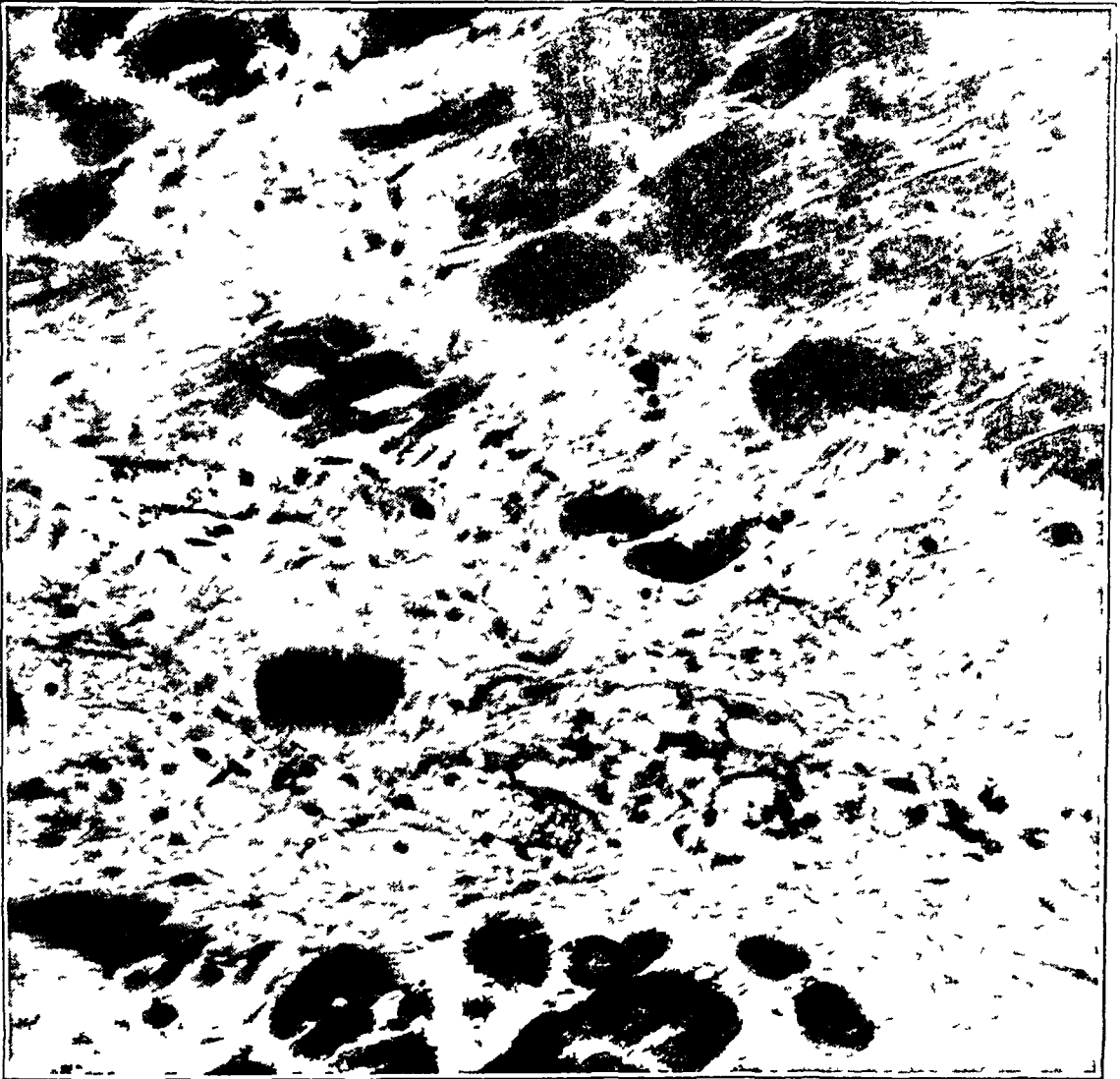


Fig 7 (case 1) —A portion of a myocardial lesion containing a group of shrunken fat cells and engorged capillaries. Eosin-methylene blue stain,  $\times 300$ .

to place, areas of fibrous tissue, similar to that in the myocardium, were found in the epicardial fat. These were directly continuous with scars in the myocardium and seemed to be due to the spread of a process originating within the musculature (fig 4). The coronary arteries presented little intimal thickening, and no atheromatous deposits were encountered.

**Lungs.** In most areas the only abnormality was vascular congestion and a slight increase in the perivascular connective tissue. There were a few regions in which the connective tissue of alveolar walls and interlobular septums was strikingly increased (figs 8 and 9). In these regions vascular engorgement was marked. Large numbers of mononuclear cells were encountered in the alveoli, some of which contained hemosiderin. Many red cells were present in these alveoli but polymorphonuclear leukocytes were not encountered. The bronchi

The alimentary tract, pancreas, gallbladder, kidneys, adrenals, uterus, ovaries, venae cavae, ribs, vertebrae, breasts, parathyroids, brain, pituitary and spinal cord did not show any significant changes on gross and microscopic study.

*Microscopic Examination*—Heart Sections taken from the regions in which white streaks were noted grossly showed areas of fibrosis unusual in character. These areas were most numerous just beneath the epicardium, but they also were encountered in midmyocardium and under the endocardium. Medium-sized arteries were often included in the areas of fibrosis, but the fibrosis was not always perivascular in position. These arteries showed little evidence of intimal thickening. There was no medial degeneration or atheromatous deposits.

The connective tissue in the areas of fibrosis was composed of delicate collagen fibers with numerous fibroblasts (fig 5). From place to place, fat cells, singly or in groups, were encountered in the connective tissue (fig 7). There were no hemosiderin deposits or infil-



Fig 6 (case 1)—A photomicrograph showing the relation of a myocardial lesion to the surrounding musculature. The edges of the scar are irregular, and its connective tissue blends with that of the adjacent myocardium. Scattered muscle fibers persist within the lesion. Eosin-methylene blue stain,  $\times 150$ .

tration with inflammatory cells. Occasional myocardial fibers persisted within the areas of fibrosis (fig 6). Many of these fibers were morphologically normal but were completely isolated by connective tissue. Other isolated fibers showed various stages of degeneration. The scars were unusually vascular (fig 5), numerous capillaries being found among the connective tissue fibers. They were thin walled and engorged with blood, often markedly so. The tissues of the scars, in consequence, bore more resemblance to granulation tissue than to scars due to arteriosclerosis or to old myocardial infarction. The process was regarded as one of gradual replacement of muscle fibers by fibrous tissue. The atrophy of muscle fibers appeared to be the result of compression and strangulation by the overgrowth of col-

matory cellular infiltration did not accompany these changes. However, there were scattered lymphocytes and a few polymorphonuclear leukocytes in the connective tissue in other areas. Perivascular collars of lymphocytes were noted about a few small vessels. Sections of the musculature of the central portions of the diaphragm and of several other muscles did not show any deviation from normal.

**Skin** The epidermis and the appendages of the skin were normal. Throughout the *pars papillaris* and the *pars reticularis* a marked increase of dense collagenous connective tissue was present. There was conspicuous fragmentation of the elastic tissue of the cutis. The subcutaneous fat was divided into lobules by rather broad and dense bands of collagenous connective tissue. The changes were those of the late stage of scleroderma.

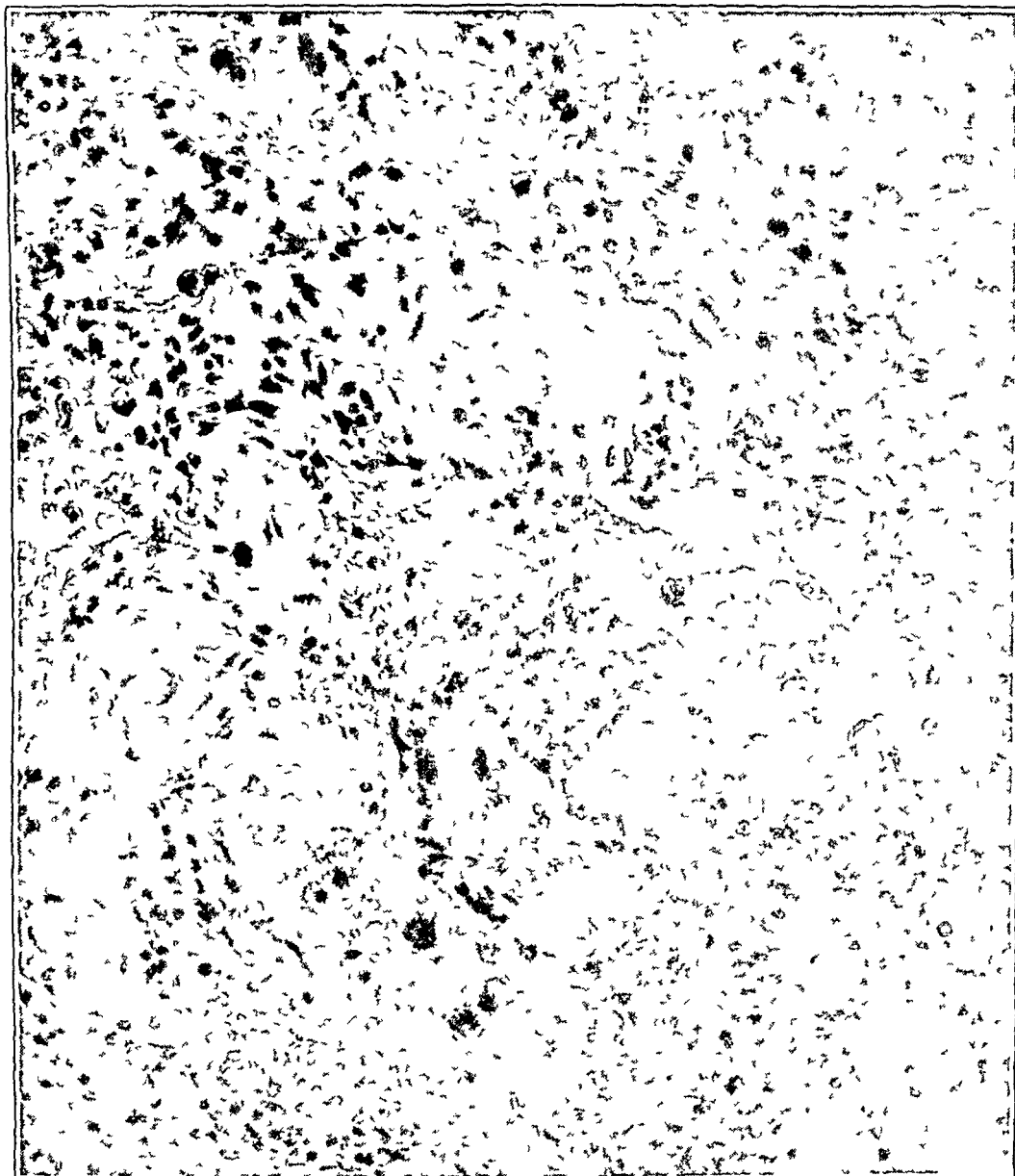


Fig 9 (case 1)—An area of extensive fibrosis in the lung. The alveoli are widely separated from one another. They contain phagocytic cells filled with pigment. Hematoxylin-eosin stain,  $\times 300$ .

**CASE 2**—A N, a white widow aged 56, was admitted to Boston City Hospital in September 1937.

During the preceding year she had been weak and had lost about 20 pounds (9 Kg) in weight. For a few months before admission she had been bothered by pains in both knees and moderate dyspnea on exertion. Later she had felt somewhat feverish in the late afternoon and had had a constant ache in the lower part of the back. This had been accompanied at times by dysuria, frequency of urination and nocturia. There was slight orthopnea at this time but no other cardiovascular symptoms. Physical examination on admission to the hospital revealed only a few rales at the bases of both lungs, a questionably enlarged heart

were normal. There was moderate thickening of the pleura by dense connective tissue. The walls of blood vessels were free from sclerotic changes.

**Spleen** The splenic sinusoids were much engorged, and the red pulp was largely depleted of lymphocytes. There was a considerable increase of the connective tissue among the sinuses. In contrast, the malpighian corpuscles were discrete, large and numerous. Moderate thickening and hyalinization of the arterioles and of the intima of larger arteries were noted.

**Liver** In the central zones of lobules, especially in the subcapsular region, the sinusoids were markedly engorged, with destruction of intervening liver cord cells. The strands of endothelial cells remained, but there was no definite increase in connective tissue. The peripheral portions of the lobules were well preserved.

**Thyroid** The acini were small, and only a few of them contained colloid. For the most part the lumens were filled with desquamated epithelium. Numerous Hurthle cells were

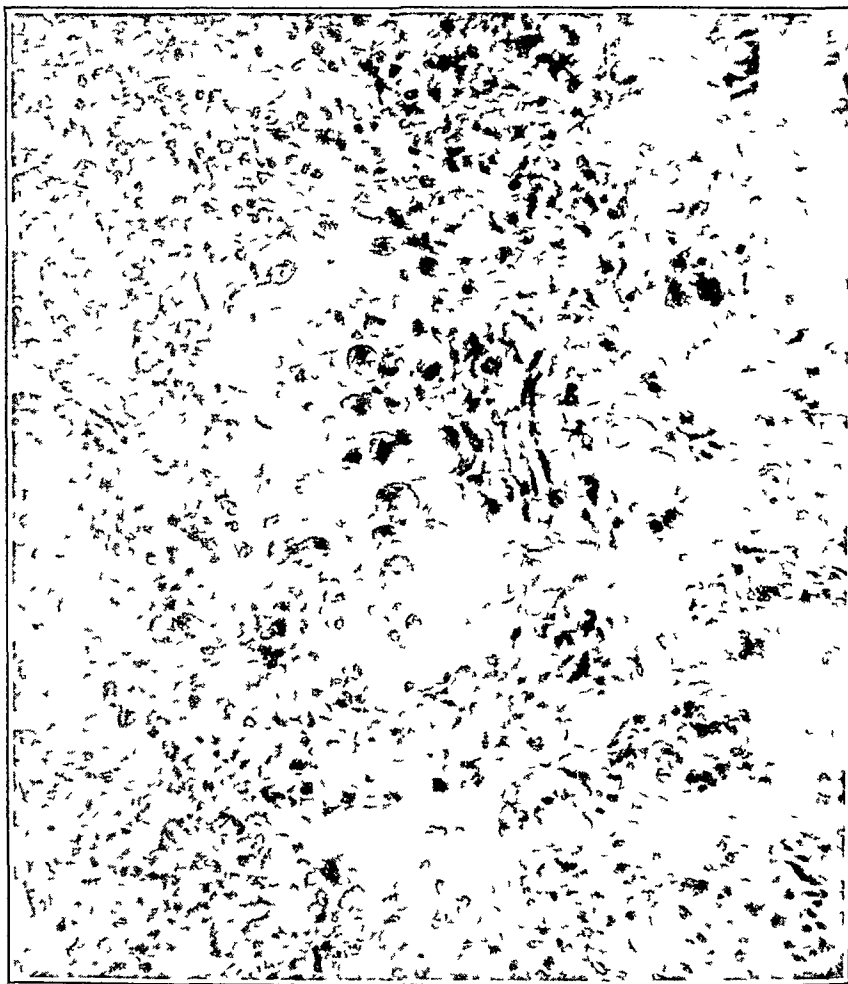


Fig 8 (case 1) —Thickening of the alveolar septums in the lung. Hematoxylin-eosin stain;  $\times 300$

present. There was considerable increase in the interstitial connective tissue. Throughout the sections marked lymphocytic infiltration was present, and lymphoid follicles were observed in many areas.

**Aorta** There was no atheroma. The elastic tissue was normal in amount and in distribution. Slight myxomatous degeneration of the media was noted.

**Voluntary Muscles** Sections from the upper intercostal muscles and the crura of the diaphragm showed conspicuous alterations. Normal muscle fasciculi alternated with fasciculi in which the individual muscle fibers were small and shrunken. In these abnormal fibers the nuclei were closer together than usual, the striations were well preserved in most instances. There was an increase in the connective tissue among the fibers, although the connective tissue between fasciculi was normal in amount. In most of the tissue inflam-

# Summary of Clinical Data

Case No	Sex	Age at Onset of Scleroderma	Age at Onset of Cardiorespiratory Symptoms	Course of Illness	Raynaud's Syndrome	Visceral Symptoms										Physical Examination					Laboratory Data			
						Arthritis	Pigmentation	Dyspnea	Orthopnea	Thoracic Pain	Cough	Edema	Gastrointestinal Symptoms	Cardiac Enlargement	Murmur	Gallop	Pulmonary and Aortic Second Sounds	Usual Arterial Pressure, Systolic/Diastolic, in mm of Hg	Lungs	Subcutaneous Edema	Electrocardiogram	Roentgenogram	Blood Levels, per 100 Cc	Basal Metabolic Rate, %
1	F	24	26	Died at 27	+	+	+	+	+	0	+	+	+	+	Slight apical systolic	+	P <sub>2</sub> = A <sub>2</sub>	140/100	Basal rates	+	Abnormal	Heart enlarged lungs congested	Total protein 6.7 Gm Albumin 3.3 Gm Globulin 3.4 Gm Calcium 10.2 mg	3+
2	F	53	54	Died at 55	+	+	+	+	+	+	+	+	+	+	Slight apical systolic	+	?	140/ 90	Basal rates	+	Abnormal	Heart enlarged	Total protein 5.6 Gm Albumin 3.0 Gm Globulin 2.6 Gm Calcium 8.0 mg	
3	F	29	48	Living at 55	+	+	+	+	+	0	0	+	+	+	0	0	P <sub>2</sub> > A <sub>2</sub>	165/ 85	Basal rates	+	Abnormal	Heart enlarged, mottling of pulmonary field, esophageal stricture	Total protein 8.1 Gm	
4	M	46	44	Died at 46	0	+	+	+	+	0	+	+	0	+	0	+	P <sub>2</sub> > A <sub>2</sub>	140/ 90	Basal rates	+	Abnormal	Heart enlarged, mottling of pulmonary field	Total protein 7.6 Gm Albumin 3.0 Gm Globulin 4.6 Gm Calcium 10.5 mg	+13
5	F	41	39	Living at 54	+	+	+	+	+	+	+	+	0	+	Mod-erately loud apical systolic	0	P <sub>2</sub> > A <sub>2</sub>	130/ 90	Basal rates	+	Abnormal	Heart enlarged, lungs congested	Total protein 7.3 Gm	
6	F	40	45	Died at 47	+	0	+	+	+	+	+	0	+	+	0	0	P <sub>2</sub> > A <sub>2</sub>	120/ 76	Basal rates	+	Abnormal	None obtained	Total protein 7.1 Gm Albumin 4.3 Gm Globulin 2.8 Gm Calcium 11.3 mg	-13
7	M	62	62	Died at 63	0	+	+	+	+	0	0	+	0	+	Slight apical systolic	0	?	110/ 70	Basal rates	+	Abnormal	None obtained	Calcium 8.7 mg Cholesterol 188 mg	
8	F	25	29	Died at 29	+	+	+	+	+	+	0	+	0	+	0	0	?	120/ 70	Basal rates	+	None obtained	None obtained		-3
9	F	19	? 30	Living at 35	+	+	+	0	0	0	0	+	+	+	Slight apical systolic	0	P <sub>2</sub> = A <sub>2</sub>	120/ 60	Clear	+	Abnormal	Heart enlarged constriction of esophagus	Cholesterol 214 mg	-22

\* Protodiastolic

† Presystolic



and slight tenderness of both knee joints. The laboratory data were not remarkable. Roentgen examination showed evidence of cardiac enlargement and early hypertrophic arthritis of the knee joints. While the patient was in the hospital her temperature remained elevated and she had mild leukocytosis. Signs of a small pleural effusion appeared on the right side, and on thoracentesis clear, yellow fluid with a specific gravity of 1.015 was obtained. This fluid contained 3,300 white cells (54 per cent polymorphonuclear leukocytes and 46 per cent lymphocytes), and the protein content was 3.3 Gm per hundred cubic centimeters. The patient was digitalized and was discharged after six weeks' hospitalization. On discharge she still had a few rales at the base of the right lung and a slight fever.

After leaving the hospital she remained in bed most of the time, feeling weak and dyspneic. The pains in the joints remained minimal. Coldness, pain and stiffness of the hands, particularly on exposure to the cold, appeared about February 1938. In May coldness and blueness of the toes were noted, associated with pain in the shoulders and knees. There were also slight edema of the ankles and a chronic nonproductive cough at this time. During the next month occasional bouts of vomiting, orthopnea and mild shooting pains across the chest appeared, and she was readmitted to the hospital in June.

Physical examination at this time revealed a brownish tinge to the skin, particularly around the neck. Over the hands and forearms the skin was thickened and tightly bound down to the underlying structures. There were similar, but less pronounced, changes in the feet. The fingers and toes were cyanotic and cool. Examination of the retinas revealed nothing remarkable except for a small whitish area just above the optic disk on the right side. There was slight dulness at the base of the left lung posteriorly and moist rales at the bases of both lungs. The heart was enlarged to the left. There was a soft, blowing systolic murmur at the apex and a protodiastolic gallop sound. Along the left sternal border, best heard in the third interspace, there was a to-and-fro sound, interpreted as a friction rub. The rhythm was regular, and the arterial tension was 160 systolic and 110 diastolic. The edge of the liver was felt about 3 cm below the costal margin. There was slight edema of the ankles.

Repeated urinalyses showed the specific gravity to be as high as 1.032. Most specimens of urine contained considerable albumin, a varying number of white cells and occasional hyaline and granular casts. The red cell count and hemoglobin level were normal, and the white cell count was 23,000 on admission. The results of other laboratory procedures are recorded in the table. The vital capacity was 700 cc. Roentgen examination of the chest revealed the heart to be symmetrically enlarged and the pulmonary fields clear. Later roentgenograms showed congestive changes in the lungs. Electrocardiograms showed changes indicative of partial heart block and low electromotive force. The patient continued to have mild elevation of temperature. Her symptoms persisted and she grew gradually worse and died in June, 1938.

*Anatomic Diagnoses*—The anatomic diagnoses included scleroderma, myocardial fibrosis, pulmonary fibrosis, bilateral focal bronchopneumonia, chronic passive congestion of viscera, bilateral hydrothorax and multiple venous thromboses.

*Autopsy*—The body was that of a well developed and well nourished woman. There was slight edema of the ankles and the face. Over the fingers the skin was stretched tightly, and the subcutaneous tissues of the region showed slight atrophy.

The peritoneal cavity contained 800 cc of slightly cloudy, amber fluid. The peritoneal surfaces were smooth and glistening.

The right pleural cavity was largely obliterated by dense fibrous adhesions with clear, amber fluid in the spaces formed by the adhesions. There were similar fibrous adhesions over the upper lobe of the left lung. Eight hundred cubic centimeters of slightly cloudy, amber fluid was present in the lower portion of the left pleural cavity.

The pericardial cavity contained 100 cc of slightly amber fluid. The surfaces were smooth and glistening.

The heart weighed 500 Gm. There was a moderate amount of subepicardial fat. The left ventricular myocardium measured 1.4 cm in thickness, the right ventricular myocardium, 0.3 cm. The myocardium was soft in texture and light red in color, speckled with gray translucent areas less than 0.3 cm in diameter. The endocardium, including the valves, was smooth. Just above the cusps of the aortic valve were several small calcified plaques. There was no narrowing of the orifices of the coronary arteries, and the lumens were normal in color, although scattered atheromatous plaques were present in their walls.

The right lung weighed 670 Gm, the left one, 380 Gm. There were patches of bronchopneumonia throughout both lungs, most extensive in the middle and the lower lobe of the right lung. No areas of fibrosis were apparent on gross examination.

The spleen weighed 310 Gm. Externally, the organ was firm, smooth and grayish purple. The cut surface was dark purple, the pulp scraped away with difficulty.

The thyroid appeared normal on gross examination

There were multiple venous thromboses. The subclavian, external jugular, internal jugular, innominate and brachial veins of the right side were filled with soft, unorganized thrombi. The right carotid sheath was thickened and adherent to the structures contained within it.

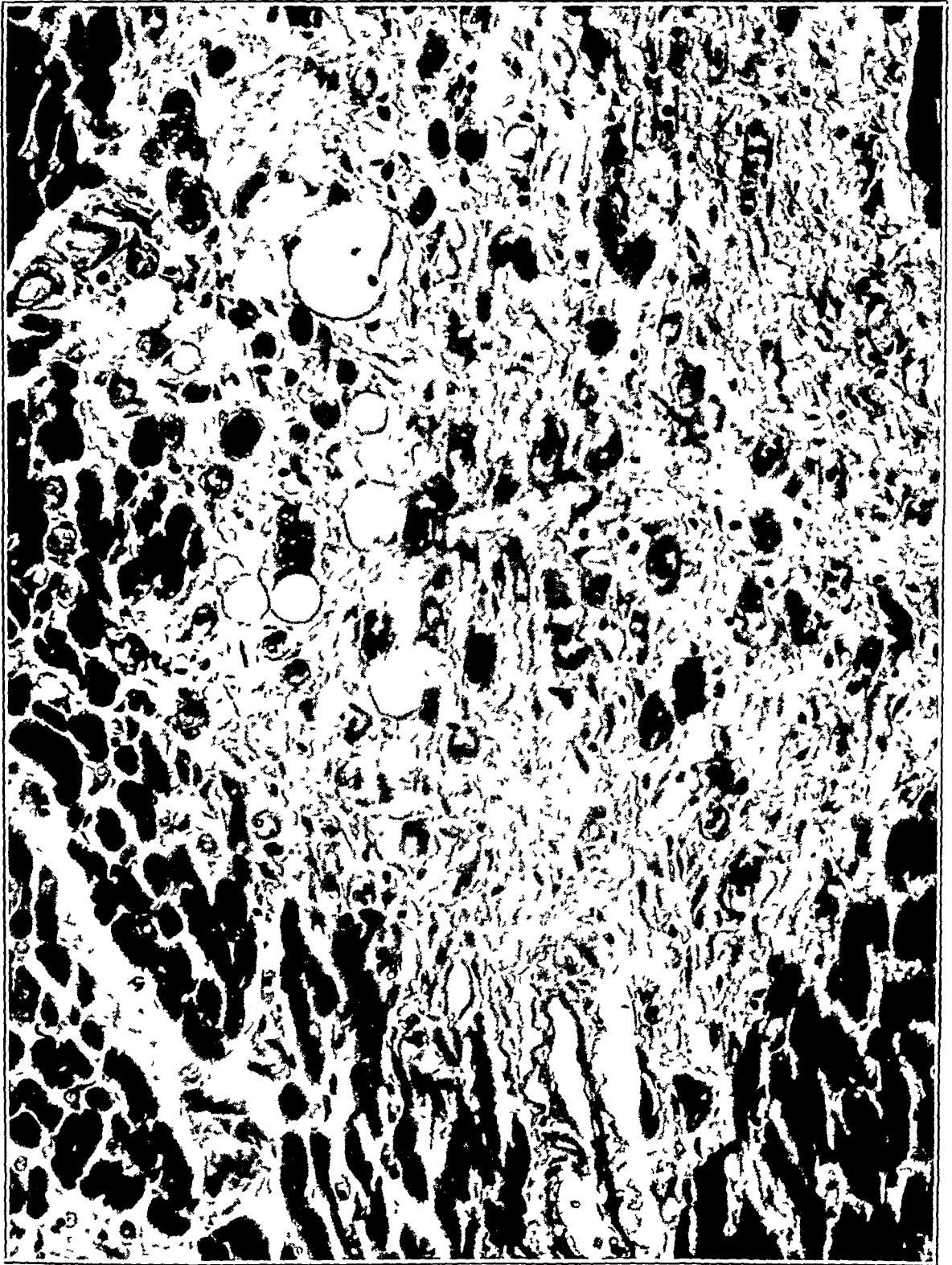


Fig 11 (case 2)—A myocardial lesion composed of highly vascular collagenous tissue. A few fat cells and muscle fibers persist within the lesion. The resemblance to the lesions in case 1 is striking (figs 5, 6 and 7). Phloxine-methylene blue stain,  $\times 300$ .

particularly the internal jugular vein. The left subclavian vein contained a friable thrombus, as did the right greater saphenous vein. There were organized thrombi in the left femoral and external iliac veins.

The liver weighed 1,520 Gm. The external surface was dark reddish brown. Surfaces made by cutting showed prominent dark red areas at the centers of the lobules contrasting with light gray or yellow portal areas.



Fig 10 (case 2)—A survey photomicrograph to show the extent and distribution of the myocardial lesions. Phloxine-methylene blue stain,  $\times 11$ .

There was a healed stellate laceration of the cervix uteri.

A few scattered patches of atheroma were present in the aorta and slightly more extensive in the abdominal region.

fibers within the areas of fibrosis were atrophic, but more often they were morphologically normal. Giant cells were not seen. The musculature between the lesions was well preserved. The lesions were of different sizes and therefore were presumed to be of different ages. The smallest lesions consisted of an increase of fibrous tissue among morphologically normal myocardial fibers (fig 12). From the study of lesions of various sizes, it was judged that the sequence involved in the development of the lesions was a progressive increase in highly vascularized connective tissue with concomitant disappearance of myocardial fibers. There was no evidence of a primary degeneration of muscle with repair.

This interpretation of sequences was strengthened by the behavior of fat cells within certain of the lesions. Most of the areas of involvement were devoid of fat, but some of them contained a few adult fat cells, usually in groups (fig 11). In some places in which the myocardium was less involved small groups of fat cells were found in the septums between the muscle bundles. That is, there was a mild degree of fat infiltration of the myocardium. Within some of the groups of fat cells the delicate, cellular fibrous tissue made its appearance in the same manner as in the smallest lesions among the muscle fibers. All stages could be found between such early lesions in the interfascicular fat and the large areas of fibrosis containing a few fat cells.

The fibrosis extended into the subepicardial fat in areas continuous with regions of fibrosis in the underlying muscle (fig 13). There were no lesions confined wholly to the epicardium. The connective tissue just beneath the mesothelial surface was normal in amount. Slight intimal thickening of the coronary arteries was included in the histologic sections, but no narrowing of the lumen, atheromatous deposits or thrombi were seen.

The endocardium was normal in thickness. At several points the subepicardial connective tissue blended with that of the areas of fibrosis in the underlying myocardium.

**Lungs** The pleura was moderately thickened, and its blood vessels were congested. There was acute bronchopneumonia. In addition, changes antecedent to the bronchopneumonia were present in focal areas. These regions were characterized by patches in which the alveolar walls were thickened because of an increase in coarse collagenous connective tissue. Stages could be traced from small focal thickenings of the alveolar basement membrane to connective tissue overgrowth so great as to reduce the alveolar lumens almost to obliteration. Lumens in regions of most marked fibrosis showed conspicuous cuboidal alveolar epithelium and were filled with phagocytic cells containing brown, granular pigment. The increase in connective tissue was accompanied by infiltration with numerous lymphocytes, moderate numbers of mononuclear cells and rare plasma cells. Infiltrating cells of similar character were present about the bronchi and some of the blood vessels in the relatively normal portions of the lung, as well as in the areas of fibrosis. The peribronchial and the perivascular connective tissue was increased in amount and highly vascular. Throughout the lungs, the arteries presented striking thickening of their walls, with diminution in caliber of their lumens. The increase in width of the wall was due to a concentric fibrous tissue thickening of the intima with fibrosis. This change involved arteries of all sizes, from the largest vessels to the small arterioles. There was no diminution in caliber of the veins, and their walls were well preserved with the exception of the increase in connective tissue about them, as previously described.

**Spleen** There was marked chronic passive congestion. Moderate arteriolar sclerosis was present, though the walls of the larger arteries were essentially normal.

**Pancreas** Moderate fatty infiltration was present, but the connective tissue was not definitely increased. The arterioles showed slight sclerosis.

**Liver** There was marked chronic passive congestion, the connective tissue of the lobules and the periportal areas was normal in amount and in character.

**Kidney** Some of the medium-sized arteries showed intimal thickening with atrophy of renal parenchyma and increase in connective tissue in the corresponding regions. There were no alterations in connective tissue which could not be accounted for as consequences of the vascular lesions. The arterioles were sclerosed in occasional instances. Moderate chronic passive congestion was also present.

**Thyroid** The connective tissue was considerably increased rather uniformly throughout the section. Foci of lymphocytes were found in the connective tissue, but there were no germinal centers. The thyroid follicles were small and the amount of colloid reduced. There was no desquamation of the epithelium, the acini being lined by an intact, uniform layer of cuboidal cells.

**Skin** Sections were taken from the abdomen and the forearm. There was a marked overgrowth of dense collagenous connective tissue of the cutis and the subcutis. This overgrowth of connective tissue extended into the subcutaneous fat along the septums between fat lobules. The elastic tissue was relatively decreased in amount, fragmented and degenerated in places. A few foci of lymphocytes and mononuclear cells were present in the lower cutis. Blood vessels were few and rather small in caliber. The epidermis was somewhat atrophic.

The gastrointestinal tract, pancreas, gallbladder, bile ducts, kidneys, adrenals, urinary bladder, fundus uteri, ovaries, parathyroids, larynx, brain and middle ears were normal

*Microscopic Examination*—Heart The most conspicuous lesions were irregular areas of connective tissue proliferation in the myocardium. These were distributed irregularly through the musculature, being encountered from endocardium to epicardium, they extended into papillary muscles (fig 10). The lesions at times bore no relation to medium-sized or large arteries but at others included such vessels within the fibrous tissue. The arteries showed none or at most only slight intimal or medial thickening. None was occluded, and the lumens did not appear narrowed. The centers of the lesions were composed of collagenous connective

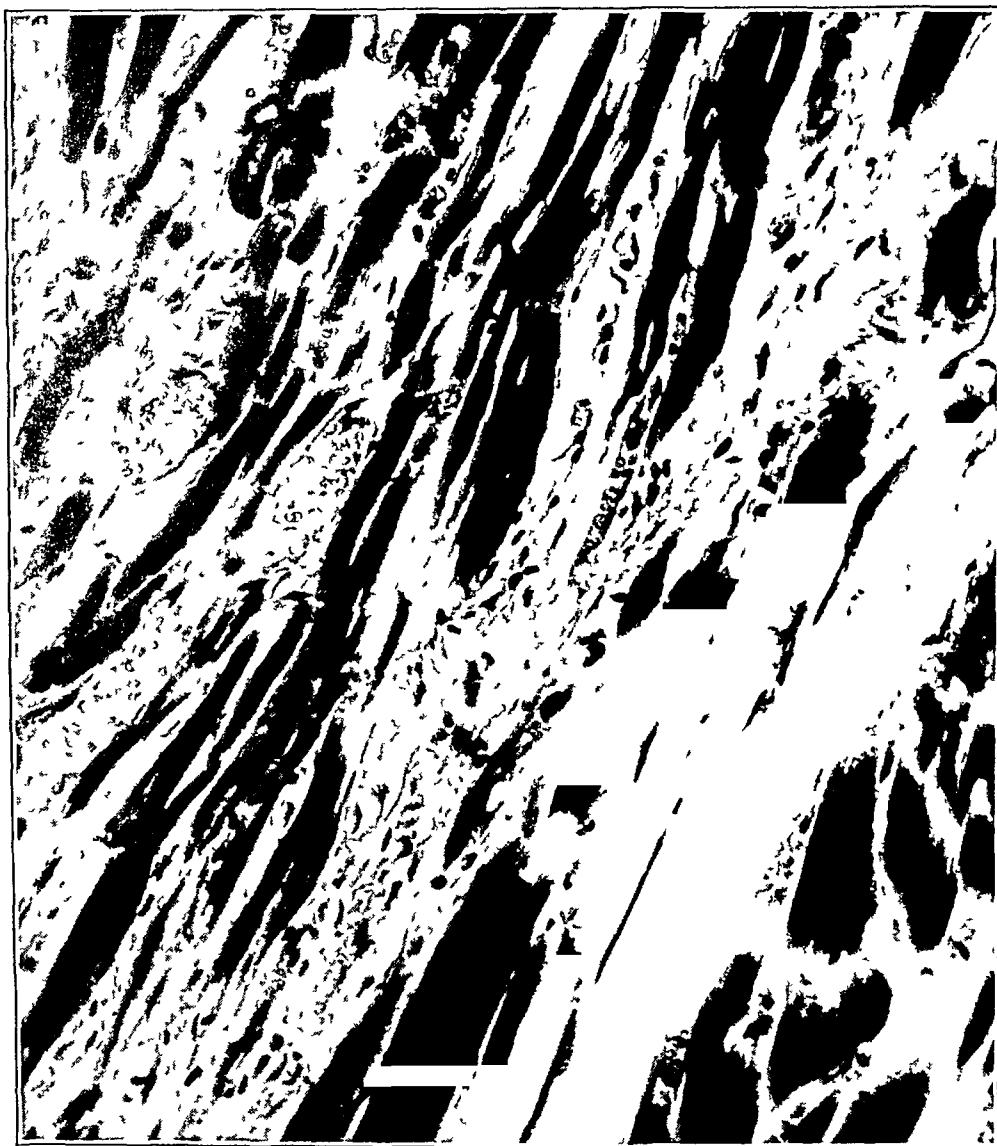


Fig 12 (case 2)—The small myocardial lesion is composed of cellular collagenous tissue among somewhat atrophic muscle fibers. Phloxine-methylene blue stain,  $\times 300$

tissue, delicate in texture. The collagen fibers were thin and somewhat separated from one another. In proportion to the number of fibers, the fibroblasts were numerous (fig 11), but lymphocytes and mononuclear cells were encountered rarely and in only a few foci. The appearance of cellularity in the areas of fibrosis seen under low magnification was due to the number of connective tissue cells rather than to inflammatory cell infiltration. No hemosiderin deposits were observed. In all areas of connective tissue proliferation, there were many thin-walled capillaries, which were distended with blood (fig 11).

The lesions were not sharply delimited. At their centers muscle fibers were usually absent, though occasional ones were encountered from place to place, at the periphery the connective tissue gradually became less and the muscle fibers more numerous. At times, the muscle

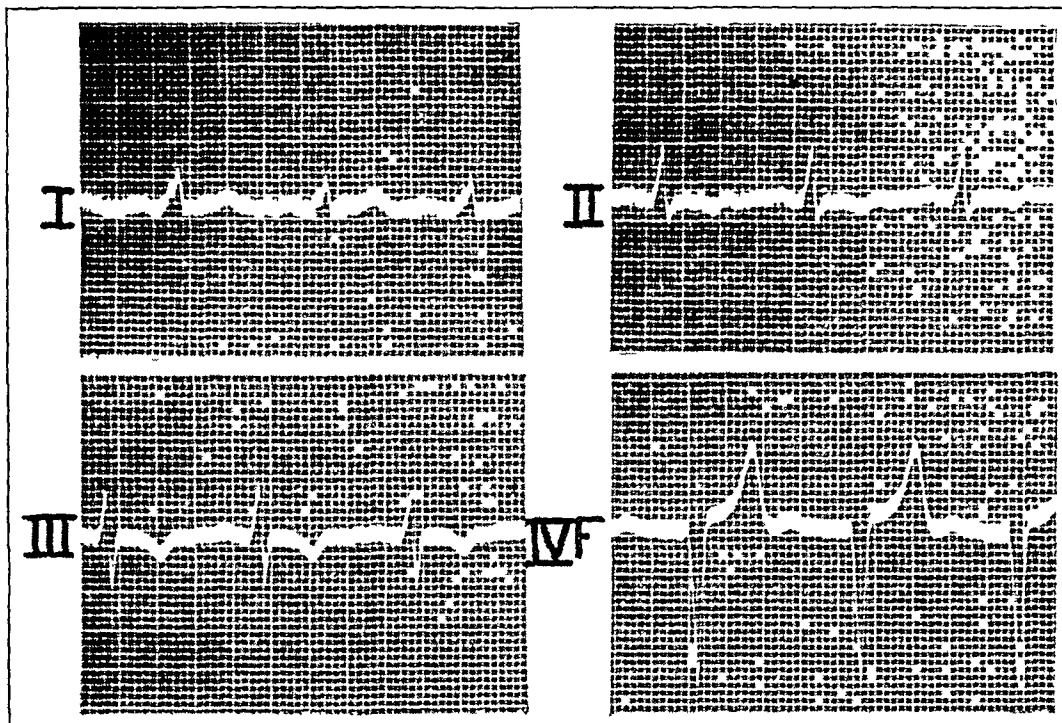


Fig 14 (case 3)—An electrocardiogram

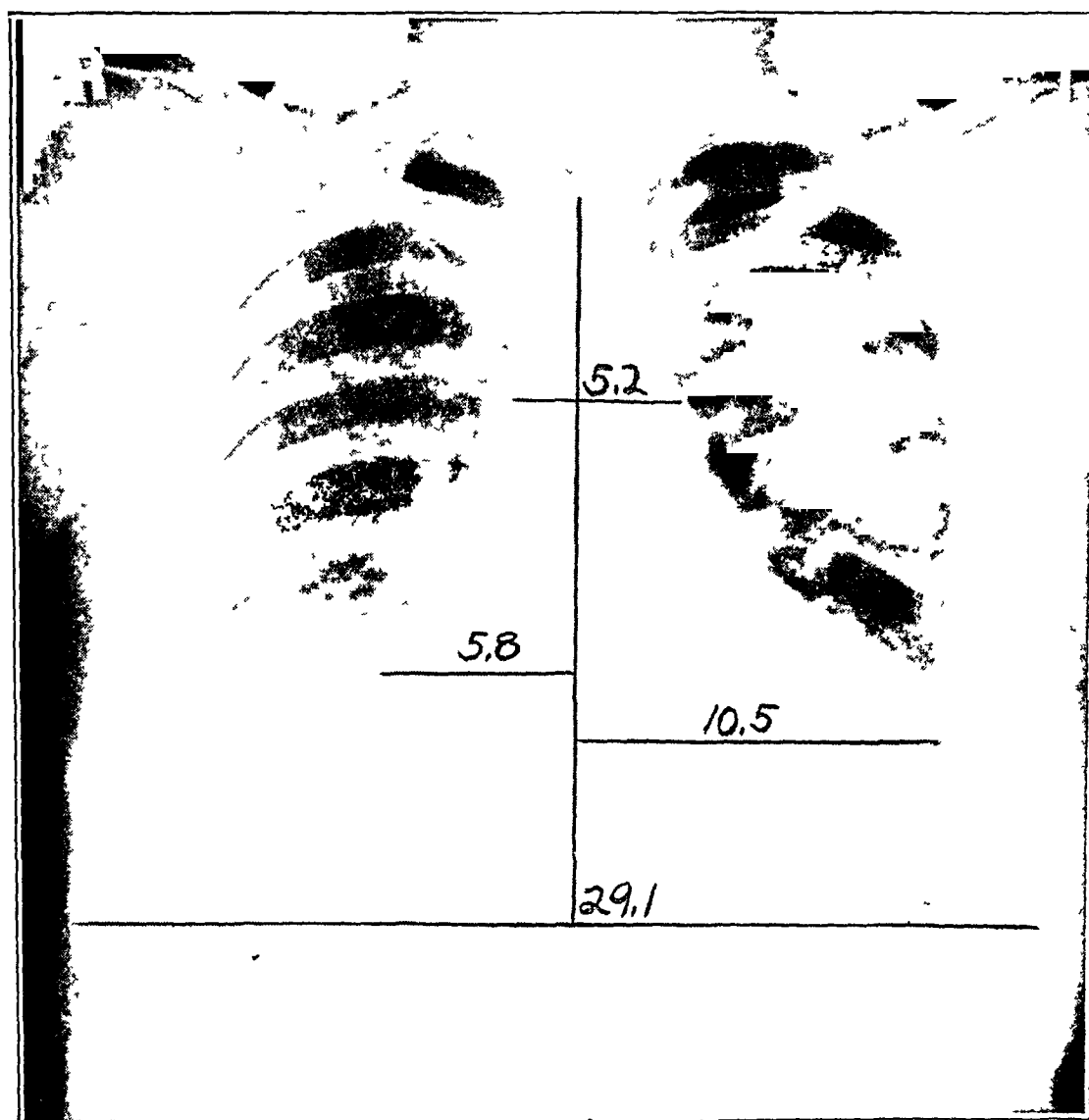


Fig 15 (case 3)—A roentgenogram of the chest There is marked cardiac enlargement  
The bases of the lungs are mottled

and showed slight hyperkeratosis, though the rete pegs were preserved. The appendages of the skin were essentially normal.

The skin of the forearm was similarly altered but to a lesser degree. The changes were interpreted as those of scleroderma.

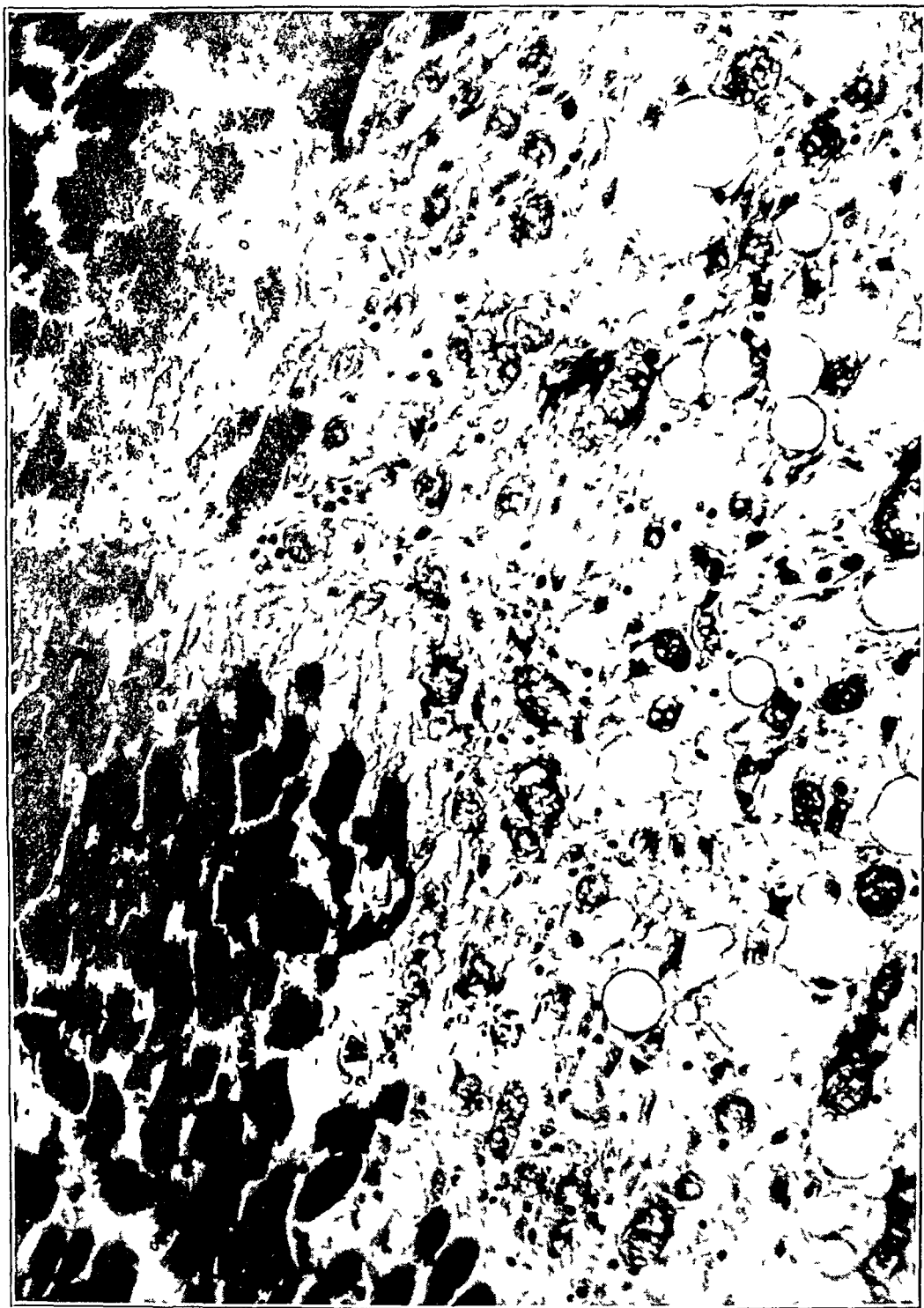


Fig 13 (case 2) —A lesion in the superficial portion of the myocardium extending into the subepicardial fat. Phloxine-methylene blue stain,  $\times 300$ .

**Pituitary** There was extensive invasion of the posterior lobe of the pituitary by basophilic cells. The gland was otherwise free from change.

**Miscellaneous** The adrenals, fundus uteri, ovaries, parathyroids, lymph nodes, vertebral marrow, sternal marrow, peripheral nerves and brain were essentially normal.

of fair quality, and there were no murmurs. The pulmonic second sound was accentuated. The blood pressure varied between 150 systolic and 80 diastolic and 180 systolic and 90 diastolic. The lungs were clear except for a few inspiratory rales at both bases. The laboratory data were not remarkable except for a total serum protein of 8.1 Gm per hundred cubic centimeters. Electrocardiograms showed changes indicative of intraventricular block (fig 14) and later of left bundle branch block.

Roentgen examination showed marked cardiac enlargement with the left border of the heart reaching the axilla (fig 15). The heart was triangular in appearance. There was a beat of small amplitude on all borders. No auricular enlargement was seen. There was a coarse mottling at the bases of both lungs, without any other pulmonary abnormalities. Examination of the esophagus showed a smooth constriction about 4 cm above the diaphragm and about

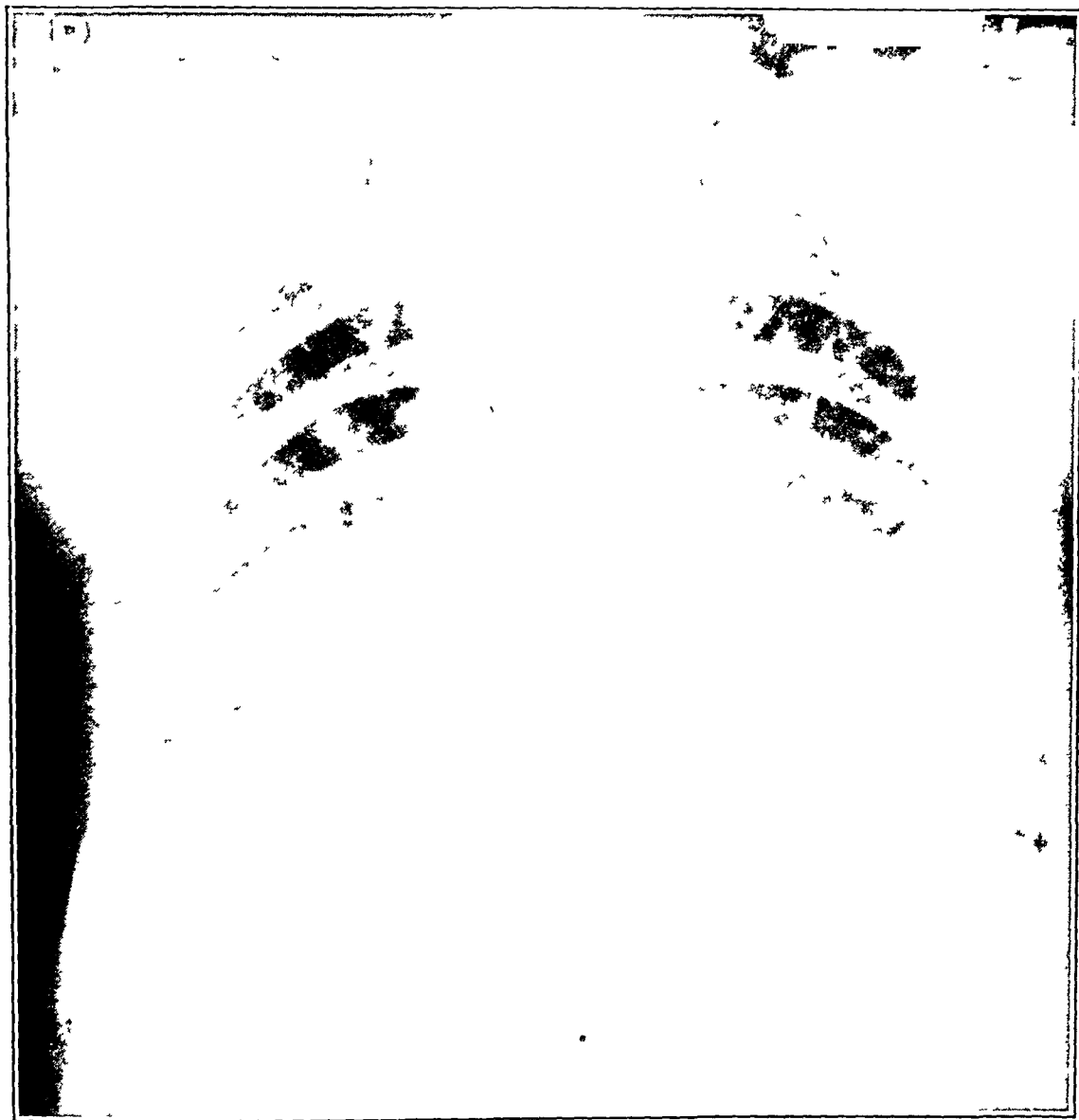


Fig 17 (case 4)—A roentgenogram of the chest. The heart is enlarged to both right and left with hypertrophy of the right ventricle and a poor, barely visible beat. There is a diffuse mottling in the middle and the lower third of the lungs.

4 mm in diameter (fig 16). It did not relax after the inhalation of amyl nitrite. The stomach, duodenum and colon appeared normal on roentgen examination. Esophagoscopy confirmed the roentgen finding, and biopsy failed to reveal any abnormalities. The esophagus was dilated several times, and the patient's ability to swallow food was improved. When last seen in April 1942, she was able to eat a normal diet without any difficulty.

CASE 4—C. P., an unemployed man aged 56, was admitted to Peter Bent Brigham Hospital in 1939.

In 1915 he had worked in an "iron mine" for six months. In 1937 he was admitted to Boston City Hospital because of pains in the wrists, shoulders, hips, knees and ankles. At



CASE 3—F W, a Russian housewife aged 54, entered Peter Bent Brigham Hospital in 1941 because of difficulty in swallowing of several years' duration

In 1916 she was first seen in the outpatient clinic of this hospital because of swelling of the hands associated with cyanosis and coldness of the hands and feet when exposed to cold. This process became worse, and soon the changes of scleroderma appeared in her face, arms and legs. About 1930 she began to have dyspnea on exertion and in 1934 began to have intermittent palpitation and edema of the ankles. There had been occasional bouts of marked difficulty in breathing and slight orthopnea for several years. There was no precordial pain.

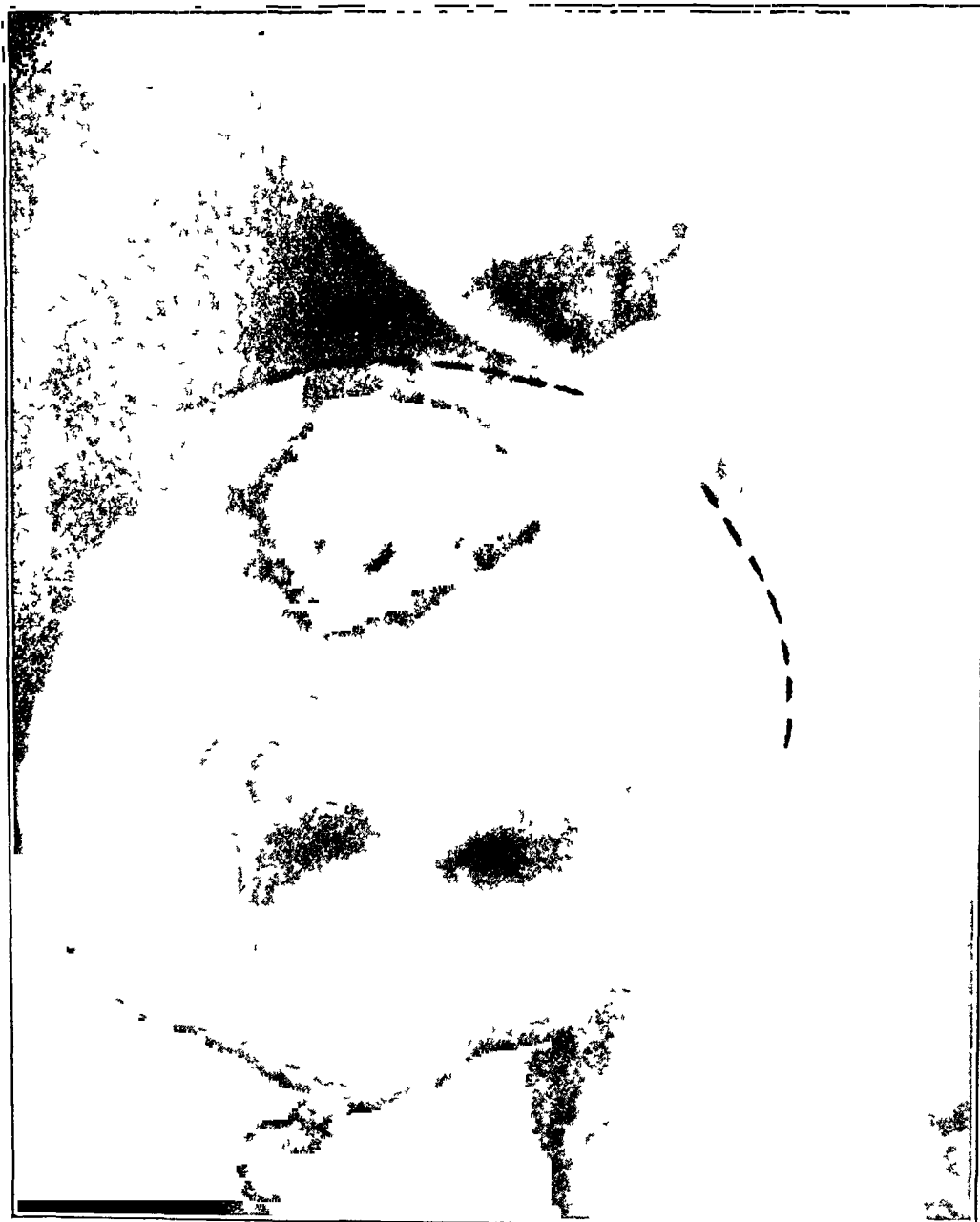


Fig 16 (case 3)—A roentgenogram of the esophagus filled with barium sulfate. There is a smooth constriction about 4 cm above the diaphragm. The roentgenogram was reversed in reproduction.

In 1938 a new symptom appeared. She noticed difficulty in swallowing and a sensation of food sticking in her chest. There was frequent regurgitation. This became slowly worse, at times interfering with swallowing liquids. Because of this the patient was admitted to the hospital.

Physical examination on admission revealed marked sclerodermatous changes of the skin of the face, arms and legs. The hands were clawlike, and there were trophic lesions on the finger tips. The heart was markedly enlarged to the right and left. The cardiac sounds were

She was discharged from the hospital and was followed up by her local physician, who stated that in April 1937 symptoms of cardiac failure developed and death occurred a few days later

CASE 7—L C, a man aged 63, was admitted to Boston City Hospital in 1939 because of inability to speak and weakness of the left side of the body

In 1937 he first began to have pains in his legs, particularly about the knee joints, and about eight months before admission he first noted cutaneous changes of a sclerodermatous nature on his legs. Although he had been slightly short of breath for years, he became much more so five weeks before entry, and one week before admission he awoke with weakness of the left side of his body and inability to speak. Physical examination showed evidences of a left hemiplegia and tight shiny skin of a sclerodermatous nature about the knees and elbows in particular, with a blotchy brown pigmentation. The heart was enlarged, the rhythm was regular, and there was a slight apical systolic murmur. The arterial pressure was 110 systolic and 70 diastolic. There were coarse rales at the bases of both lungs. An electrocardiogram showed left axis deviation. No roentgen examination of the chest was done. The patient gradually became weaker and died after one month's hospitalization. Permission for post-mortem examination was not obtained.

CASE 8—M F, a woman aged 28, was admitted to Peter Bent Brigham Hospital in 1936

About three years previously, six months after childbirth, she began to experience coldness and pallor of her hands on exposure to the cold. Later the hands became purple and painful under similar conditions. In 1934 her hands became swollen, the movement limited and the skin shiny. There were no cardiac or gastrointestinal symptoms. Physical examination on admission to the hospital showed sclerodermatous changes of the skin of the entire body with deep brown pigmentation. The heart was not enlarged, the cardiac sounds were normal, and the rhythm was regular. No murmurs were heard. The arterial pressure was 120 systolic and 70 diastolic. There were fine rales at the bases of both lungs, but no other pulmonary abnormalities. The laboratory data were not remarkable. About one year after discharge she was seen by her local physician because of almost constant dyspnea, edema of the ankles and occasional pains in the chest on the left side. The results of physical examination at this time were unchanged except that the heart was enlarged. She died at home in January 1937.

CASE 9—M L, a woman aged 25, was admitted to Peter Bent Brigham Hospital for the first time in 1932.

In 1926, soon after the birth of her first child, she noted blanching of her fingers when exposed to cold. This was often accompanied by an aching pain, and soon after this the skin gradually became tight, shiny and deeply pigmented. In 1933 roentgen examination of the chest failed to reveal any abnormalities. During the following years bilateral cervical sympathectomies and thyroidectomy were performed in an attempt to alleviate her condition. In 1937 she began to have difficulty in eating, because food seemed to catch substernally. She also began to tire more easily and gradually became somewhat dyspneic on exertion. When last seen, in March 1942, her difficulty in eating had increased slightly, but there had been no recent change in her other symptoms. Physical examination at that time showed diffuse involvement of the skin with deep pigmentation. Her heart was slightly enlarged, the cardiac sounds were of good quality, and there were no murmurs. The arterial pressure was 110 systolic and 70 diastolic. Roentgen examination of the chest revealed a marked increase in the size of the heart compared with its size at the original examination in 1933. The heart had assumed a triangular appearance, and a moderately good beat was present on all borders. There was a diffuse increase in the pulmonary markings. The esophagus showed a narrow constriction over a distance of several centimeters in the lower third of the esophagus. An electrocardiogram showed only low electromotive force. Her vital capacity was 1,200 cc and the basal metabolic rate was —22 per cent. The cholesterol level of the blood was 214 mg per hundred cubic centimeters. The results of other laboratory procedures were within normal limits.

The changes in the size of the heart are difficult to evaluate in this case because of the total thyroidectomy.

#### COMMENT

In all the cases reported here the patients showed the classic picture of scleroderma together with signs and symptoms suggesting heart failure. The data are summarized in the table. In 7 of the 9 cases the patients were women. Their ages at the onset of the cutaneous changes ranged from 19 to 62 years, the average being 38 years. In 3 cases the appearance of cardiac symptoms preceded

that time he had a cough productive of yellowish, odorless sputum and had lost about 20 pounds in weight. Physical examination on admission revealed no abnormalities except stiff, slightly swollen and red joints. A roentgen examination of the chest showed diffuse mottling of the bases of both lungs and enlargement of the heart to the left with enlargement of the supracardiac area. Electrocardiograms showed evidence of partial heart block with a PR interval of twenty-six hundredths of a second. A diagnosis of cardiac decompensation of undetermined origin was made. Shortness of breath became the most prominent symptom, and in February 1938 he entered another hospital, where examination yielded similar results. After his discharge from that institution his symptoms continued to increase, and in August 1938 he came to the outpatient clinic of Peter Bent Brigham Hospital. Examination at this time showed smooth and thickened skin over the fingers. A roentgen examination of the chest showed the heart to be enlarged to both the right and the left with hypertrophy or dilatation of the right ventricle and a poor, barely visible beat (fig 17). There was a diffuse mottling of both lungs, particularly the middle and the lower thirds, with the apices fairly clear. The hilar glands appeared enlarged. Because of progressive dyspnea, cough and edema of the ankles he was admitted to the hospital in March 1939. Physical examination at that time showed sclerodermatous changes of the extremities with clubbing of the fingers. The heart was enlarged, the sounds were distant and there were a presystolic gallop and an accentuated pulmonic second sound. There were no murmurs. The arterial pressure was 140 systolic and 90 diastolic. There were moist rales at the bases of both lungs. The liver was just palpable. There was moderate edema of the legs. The laboratory data were normal. Biopsy of the skin showed changes consistent with scleroderma. Roentgen examination of the chest did not reveal any new abnormalities. After discharge from the hospital he returned periodically to the outpatient clinic. His scleroderma became more pronounced. In October 1939 roentgen examination of the heart showed considerable enlargement with a triangular shape and prominence of the pulmonary conus. He died at home on November 30.

CASE 5—D K, a woman aged 52, was admitted to Peter Bent Brigham Hospital in 1940.

In 1927 she was seen by a physician because of weakness, dyspnea and edema of the ankles. She had vague pains in the joints at that time, and in 1929 she noted for the first time that her hands turned blue, felt cold and ached on exposure to the cold. Soon after that she began to have tightness of the skin and limitation of motion of the hands. In 1939 she suffered from a sharp stabbing pain in the upper portion of the chest, on the left side, which recurred a few months later. Soon after the pain occurred, weakness, dyspnea and edema of the ankles developed. Because of these symptoms she was admitted to Peter Bent Brigham Hospital. On physical examination on admission, she was orthopneic and the skin over the face, hands and feet was tight and inelastic. The heart was enlarged with a loud high pitched systolic murmur at the apex. The pulmonic second sound was accentuated. The rhythm was absolutely irregular. Arterial pressure was 130 systolic and 90 diastolic. There was dulness at the bases of both lungs with diminished breath sounds and many moist rales. The liver was palpable just below the costal margin. Moderate edema of the ankles was present. Laboratory data were not remarkable. The vital capacity on admission was 800 cc., increasing to 1,250 cc at the time of discharge. Thoracentesis yielded fluid which contained 900 white cells, 50 red cells and 49 Gm of protein per hundred cubic centimeters and had a specific gravity of 1.018. An electrocardiogram showed auricular fibrillation, premature ventricular beats and left bundle branch block. Roentgen examination of the chest showed marked cardiac enlargement, both to the right and to the left, and the heart appeared triangular. There was an irregular beat of fair quality. No intracardiac calcification was seen. The lungs appeared congested, and there was fluid at both bases. The patient showed improvement during her stay in the hospital. In April 1942 she was reported to have continued evidence of myocardial failure, but no new symptoms had developed.

CASE 6—R G, a woman aged 46, was admitted to Peter Bent Brigham Hospital in 1936.

Seven years before she noted for the first time blanching of her fingers on exposure to cold, and one year later sclerodermatous changes appeared. In 1935 a cervicothoracic sympathectomy was performed, with only questionable improvement. For one year prior to admission she experienced palpitation and tired readily on exertion. She had occasional bouts of a "heavy" feeling in the precordial region. Physical examination on admission to the hospital showed sclerodermatous involvement of the arms and legs with deep pigmentation. The retinal vessels were normal. The heart was not enlarged, and the sounds were normal without murmurs. The rhythm was regular except for occasional extrasystoles. Arterial pressure was 120 systolic and 76 diastolic. Electrocardiograms showed left axis deviation and premature ventricular beats. Biopsy of the skin showed changes consistent with scleroderma.

all of the roentgenograms there was an increase in the pulmonary markings, this usually being most marked in the lower lobes. In several cases the lungs showed a peculiar diffuse granular or mottled appearance, particularly at the bases, extending well out to the periphery but sparing the apexes. At times the changes suggested to the roentgenologist the appearance of bronchiectasis or lipid pneumonia. In instances of heart failure hilar congestion was usually noted.

The electrocardiograms in each of the 8 cases in which they were obtained showed some abnormality. In 1 instance there was auricular fibrillation, and in 3 there were premature ventricular beats. In 3 there was abnormally low electromotive force. In 2 there was partial heart block, in another, first intraventricular block and later bundle branch block, and in a fourth instance there was left bundle branch block. In 2 instances there was left axis deviation, while in the others the electrical axis was within normal limits.

Gastrointestinal symptoms were common, appearing in 4 of the cases reported here. In case 3 there had been progressive difficulty with the passage of food through the esophagus. Roentgen examination revealed a striking constriction of the esophagus about 4 cm above the diaphragm. The constriction did not relax after the inhalation of amyl nitrite. Esophagoscopy showed a stricture, without any evidence of mucosal abnormality. Biopsy failed to reveal any abnormality. Esophageal dilatation produced complete relief. In another case (9) the patient also had difficulty in swallowing, though it was less severe, and a roentgen examination showed a smooth constriction in the lower end of the esophagus. The patient in case 1 had symptoms of esophageal dysphagia, severe enough to suggest the diagnosis of carcinoma of the esophagus on admission to the hospital. However, roentgen examination was not done before her death. Postmortem examination failed to reveal any abnormality in the esophagus.

The case histories of 36 additional patients with scleroderma, who were studied at Massachusetts General Hospital, were reviewed. Six of these patients had symptoms referable to the upper portion of the gastrointestinal tract. Roentgen examination showed constriction of the lower part of the esophagus with dilatation above in 5 of them. In the sixth there was a diffuse dilatation of the esophagus, stomach and small intestine.

The laboratory data in the cases reported in this paper were not helpful. The red cell count, the white cell count and the hemoglobin level were essentially normal in all cases. Urinalysis revealed varying amounts of albumin in most instances, as well as red cells, white cells and granular and hyaline casts on several occasions. The total serum protein levels varied from 5.6 to 8.1 Gm per hundred cubic centimeters in the 6 cases in which they were determined. The albumin varied from 3.0 to 4.3 Gm and the globulin from 2.6 to 4.5 Gm per hundred cubic centimeters. In 2 instances in which the protein content of pleural and of pericardial fluid was noted, it was unusually high for a simple transudate<sup>6</sup>. Blood levels of calcium and phosphorus were normal in the 5 cases in which they were determined, as was the blood level of cholesterol. In those cases in which the vital capacity was determined, it was found to be markedly diminished. The basal metabolic rate was within normal limits, except for a level of -22 per cent in 1 case (9) in which the patient had had a total thyroidectomy in an attempt to relieve her cutaneous condition.

The pathologic aspects of sclerodermatous involvement of the skin have been extensively studied, and observations on the skin in these cases serve only to con-

6 Paddock, F. K., The Diagnostic Significance of Serous Fluids in Disease. *New England J. Med.* **223**: 1010 (Dec. 19) 1940.

changes in the skin by as much as two years. Though there were symptoms of Raynaud's disease in 8 of the 9 cases, the degree of blanching and pain in the extremities on exposure to cold could not be correlated with the progression of the visceral manifestations of the disease. In all cases the patients complained of symptoms referable to the joints, usually mild, though in some cases severe pains in the joints with redness and tenderness suggested the diagnosis of rheumatoid arthritis. In all cases there was abnormal pigmentation, often associated with areas of loss of pigment. In general, both the progress of the cutaneous disease and its relation to vasomotor, joint and cardiac symptoms were extremely variable.

The evaluation of cardiac symptoms in scleroderma is difficult because the cardiac manifestations are frequently associated with pulmonary lesions and with involvement of the thoracic wall itself. In all of the cases reported here the patients complained of dyspnea on exertion, some even before the onset of the cutaneous changes, others not until the later stages of the disease. Orthopnea was definitely present in 5 cases, and there was a history suggestive of it in several others. There was paroxysmal nocturnal dyspnea in 2 cases. Cough, at times productive of whitish mucoid sputum, was a rather prominent symptom. In none of the 9 cases was there gross hemoptysis, but in 1 case not included in the present series the patient had massive hemoptysis, the cause of which was never determined. Pain in the chest occurred in 4 of the 9 cases. Its character varied considerably, but usually it was precordial rather than substernal and was not related to exertion. Edema of the ankles was present in all cases, and in some the edema was general. Early in the disease the edema may be associated with redness and heat, but in the later stages there was no clinical evidence of inflammatory reaction. In the 6 cases with a fatal termination, the symptoms of generalized congestion were present at the time of death. In all cases there was some evidence of cardiac enlargement on clinical examination. The cardiac sounds were either of normal or of less than normal intensity. The rhythm was regular in 6 cases, in 1 there was auricular fibrillation, and in 2 there were extrasystoles. In 1 case (2) a definite pericardial friction rub was heard. In 1 case there was a loud apical systolic murmur, and in 4 others a slight apical systolic murmur was audible, but in no instance was there a diastolic murmur. In 4 of the 6 cases in which it was specifically noted, the pulmonic second sound was accentuated and was louder than the aortic second sound. In 3 cases a prominent diastolic gallop sound was noted, in 2 it was protodiastolic in time, and in the third it was presystolic. The arterial blood pressure was moderately elevated in several cases. Even in the absence of cardiac failure, basal rales were often heard in the lungs. Hydrothorax and enlargement of the liver were frequent findings when the heart failed. In 1 case the spleen was slightly enlarged. Generalized lymphadenopathy was not noted in any case.

In the 6 cases in which roentgen examination of the chest was done, strikingly similar changes were encountered. In all there was cardiac enlargement, varying from a moderate to a marked degree. The heart was triangular in shape, and in most cases the beat was of poor amplitude. In 1 instance the supracardiac area appeared to be widened, and in another there was a prominent pulmonary conus. The roentgen findings did not suggest hypertensive or valvular heart disease. There was no detectable calcification in the valves. The left ventricle was not predominantly enlarged, and the left auricle was not unduly prominent. The combination of the triangular shape and the weak beat suggested to the roentgenologist the diagnosis of myxedema heart disease or of pericardial effusion. In

of both disorders<sup>11</sup> Here in a patient with typical scleroderma a few lesions were encountered which were suggestive but not characteristic of dermatomyositis

The changes in the liver and the spleen were those of long-standing chronic passive congestion

There were extensive alterations in the thyroid in case 1 and less striking ones in case 2 These consisted of atrophy of acinar epithelium with desquamation and colloid depletion together with increase in fibrous tissue These lesions were diffuse, not focal They are not a specific part of scleroderma but are encountered in diseases of many types No such changes were found in the thyroid in case 9, in which the gland had been removed surgically while the patient was still in good condition Although atrophy of the thyroid with colloid depletion and epithelial desquamation is more frequently encountered in children, it occurs occasionally in adults These lesions have been considered in relation to lipid nephrosis by Wolbach and Blackfan<sup>12</sup>

Our attention in this study has been focused especially on the changes in the heart and the physiologic alterations resulting from them The lesions in the heart consist of scars of unusual type These involve the myocardium, extending to the epicardium and endocardium only secondarily and then to a slight degree There are certain resemblances between these lesions and those due to vascular changes There are a number of ways, however, in which the lesions encountered post mortem in the hearts of the 2 patients with scleroderma differ from those caused by vascular disease The lesions in the myocardium in the patients with scleroderma were not in any particular relation to arteries, these structures being indifferently included in the scars or not Furthermore, the vessels were normal or showed minor intimal thickening without thrombosis or significant diminution in the caliber of the lumen The hemosiderin deposits often seen in areas of myocardial scarring due to vascular lesions were entirely absent Within the scars in the hearts of the 2 patients studied post mortem the myocardial fibers were preserved in small numbers even in the centers of the lesions (fig 6) This was true also of fat cells (figs 7 and 11) and of blood vessels The sequences were interpreted as a primary overgrowth of fibrous tissue with secondary destruction of other myocardial structures The histologic nature of the lesions is different from that of the lesions of Fiedler's myocarditis, though their distribution is similar

The connective tissue itself was rather unusual in character Fibroblasts were numerous, imparting a cellular appearance to the lesions when they were studied with low power The collagenous fibers were rather refractile but not coarse and increased in caliber, as are those of the skin in characteristic sclerodermatous lesions Within the connective tissue infiltrating the myocardium, there were large numbers of capillaries distended with red cells The lesions, then, may be characterized as focal overgrowths of cellular, vascular connective tissue with secondary degeneration of normal myocardial structures in the regions involved

Are these myocardial lesions specifically related to scleroderma or are they coincidental? In other words, are we dealing with scleroderma heart disease or with heart disease in patients who also had scleroderma? We feel that the evidence points toward the interpretation that the myocardial lesions are an integral

11 Banks, B M Is There a Common Denominator in Scleroderma, Dermatomyositis, Disseminated Lupus Erythematosus, the Libman-Sacks Syndrome and Polyarteritis Nodosa? *New England J Med* **225** 433 (Sept 18) 1941

12 Wolbach, S B, and Blackfan, K D Clinical and Pathological Studies on So-Called Tubular Nephritis (Nephrosis), *Am J M Sc* **180** 453 (Oct) 1930

firm the descriptions in textbooks.<sup>7</sup> The histologic sequences of cutaneous scleroderma seem best interpreted as dependent on change in the collagenous connective tissue. The other changes in the skin may be explained as a consequence of this alteration in the connective tissue. The collagen fibers already present become thickened, and new ones are formed. In the earlier stages, illustrated in this series particularly by case 2, the cutis and the subcutis are edematous and are infiltrated with moderate numbers of lymphocytes and mononuclear cells. These cells are in part scattered through the connective tissue and in part collected about blood vessels.

As the lesion progresses, the edema and the cellular infiltration disappear and the changes in the collagenous tissue dominate the histologic picture. The individual fibers are enormously thickened and hence, besides being increased in number, occupy more space than they did originally. Secondary to this, the epidermal layer undergoes atrophy and the rete pegs become flattened. The appendages of the skin, while retained, are rendered less conspicuous because of the increase in the connective tissue among them.

The connective tissue overgrowth is confined to the collagenous type. The elastic tissue fibers, on the other hand, become fragmented and degenerate to a variable extent as they are encroached on by the collagenous fibers. Some of the larger vessels have thickened media. The small blood vessels are few and show no changes other than diminution of caliber in their capillary beds.

Since scleroderma has been especially studied by dermatologists and since material for postmortem examination is not abundant, the changes in organs other than the skin have received less attention than they merit. In this respect, knowledge of scleroderma has developed much as it has in several other diseases involving the skin, such as lupus erythematosus and sarcoid. All these diseases, however, involve the skin only as a part of the clinical and pathologic picture which includes many organs less accessible to study by inspection. Fibrosis in the lungs,<sup>8</sup> cardiac failure<sup>9</sup> and stricture of the esophagus<sup>10</sup> have been noted in clinical case reports of scleroderma, and pathologic studies have shown that most of the organs of the body may be involved.<sup>4a</sup>

The focal areas of fibrosis in the lungs in cases 1 and 2 reported here may be related to the sclerodermatous process. It is difficult to rule out foci of chronic bronchopneumonia with organization, especially in view of the extensive lymphocytic infiltration and the peribronchial fibrosis in regions of normal alveoli. However, the distribution, corroborated by the results of roentgen examinations, would be unusual in chronic bronchopneumonia. The striking vascular lesions in the lungs in case 2 were not present in case 1. They have been observed in many patients without scleroderma. For this reason, they have not been regarded as a part of scleroderma *per se*.

Areas of atrophy and cellular infiltration were encountered in the upper intercostal muscles and the diaphragm in case 1. These are interesting in view of the possible resemblances of scleroderma to dermatomyositis. Clearcut scleroderma and clearcut dermatomyositis are distinctly different, but there are some patients who present both clinical and pathologic changes which partake of the nature

7 McCarthy, L. *Histopathology of Skin Diseases*, St. Louis, C. V. Mosby Company, 1931.

8 Murphy, J. R., Kramin, P., and Gerson, M. J. *Scleroderma with Pulmonary Fibrosis* *J. A. M. A.* **116** 499 (Feb. 8) 1941. Linenthal and Talkov.<sup>4b</sup>

9 Gitlow, S., and Steiner, S. *Scleroderma with Special Reference to the Blood Chemistry*, *Arch. Dermat. & Syph.* **9** 549 (May) 1924.

10 Rake, G. On the Pathology and Pathogenesis of Scleroderma, *Bull. Johns Hopkins Hosp.* **48** 212, 1931. Ochsner and DeBakey.<sup>4c</sup> Brock.<sup>5a</sup>

# LEUKEMIA

A CLINICAL AND PATHOLOGIC STUDY OF ONE HUNDRED AND  
TWENTYTHREE FATAL CASES IN A SERIES  
OF 14,400 NECROPSIES

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Although a voluminous literature exists on the subject of leukemia, there have been few studies dealing with a large series of cases in which autopsy was done. For this reason we have felt justified in reporting our study to correlate clinical and pathologic observations in all types of leukemia. Most studies usually deal with only one type or with one or a few of the problems of the complex subject of blood dyscrasias. This is well illustrated in the excellent monograph by Forkner<sup>1</sup> on leukemia written in 1938 and by subsequent papers on this subject. In this paper we have reviewed and critically examined 123 fatal cases of leukemia. This group was selected from 14,400 consecutive autopsies performed at the Cook County Hospital from 1929 to March 1941 and represents an incidence of 0.86 per cent. With a few exceptions data from a complete postmortem examination and studies of the peripheral blood and the bone marrow were available. We believe that such a large material and its critical review justifies this publication, the largest number of cases presented in one paper until now was 77 (Ikeda<sup>2</sup>) encountered in 12,396 autopsies.

## CLASSIFICATION

There is considerable confusion in the literature as to terminology and classification of different types of leukemia. We cannot discuss in detail the controversies regarding various types but intend to state briefly our stand on these questions. For a long time two main types have been generally recognized: myelogenous leukemia and lymphatic leukemia. Since the work of Reschad and Schilling-Torgau<sup>3</sup> and Sabin and associates<sup>4</sup> monocytic leukemia has been proved to be a definite separate entity. The so-called "Naegeli type" of monocytic leukemia and the monocytic phase of myelogenous leukemia (Downey<sup>5</sup> and co-workers) apparently represent only myelogenous leukemia with a marked monocytic reaction.

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1 Forkner, C. E. *Leukemia and Allied Disorders*, New York, The Macmillan Company, 1938.

2 Ikeda, K. Gastric Manifestations of Lymphatic Leukemia, *Am J Clin Path* **1** 167, 1931.

3 Reschad, H., and Schilling-Torgau, V. Ueber eine neue Leukämie durch echte Uebergangsformen (Splenozytenleukämie) und ihre Bedeutung für die Selbständigkeit dieser Zellen, *München med Wchnschr* **60** 1981, 1913.

4 (a) Doan, C. A., and Wiseman, B. K. The Monocyte, Monocytosis and Monocytic Leukosis, *Ann Int Med* **8** 383, 1934. (b) Sabin, F. R., Doan, C. A., and Cunningham, R. S. Discrimination of Two Types of Phagocytic Cells in the Connective Tissue by the Supravital Technique, *Contrib Embryol* **16** 125, 1925.

5 Downey, H. Present-Day Knowledge of Blood Cell Formation and Pathology, *J Iowa M Soc* **22** 477, 1932.



part of scleroderma. The sequence involved in the development of the myocardial lesions were those of overgrowth of connective tissue, as in the skin, but the character of the connective tissue in the skin and myocardium in scleroderma was different. However, the changes in the 2 patients with scleroderma studied at postmortem examination were similar and differed in several significant respects from other varieties of myocardial scars. The pathologic observations together with the clinical data in the cases of the series indicated that scleroderma heart disease is a clinical and pathologic entity.

#### SUMMARY AND CONCLUSIONS

The clinical histories of 9 patients with generalized scleroderma are reported. Postmortem examinations were performed on 2 patients. These 9 patients were selected for study because they all had symptoms and signs of heart disease. Both the clinical and the pathologic studies indicate that the sclerodermatous process is not confined to the skin but involves other organs. The cardiac failure is caused by myocardial scarring of an unusual type. Roentgen examinations may show involvement of the lungs. Dysphagia is common and esophageal stricture occurs.

These patients demonstrate that scleroderma heart disease is a clinical and pathologic entity.

Dr. N. W. Faxon, of Massachusetts General Hospital, and Drs. J. W. Manary and F. Parker Jr., of Boston City Hospital, cooperated in making several of these cases available for study.

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53 cases (43.1 per cent) of the myelogenous type, 37 cases (30.8 per cent) of the lymphatic type and 5 cases (4.1 per cent) of the monocytic type. Ikeda<sup>2</sup> reported 51 cases of myelogenous leukemia and 26 cases of lymphatic leukemia. Our percentage of cases of acute lymphatic leukemia is also higher than the figures indicated in the literature. Of the 123 cases (61 per cent), 75 represented acute leukemia, and of this number, there were 26 cases (36 per cent) of stem cell leukemia, 33 cases (44 per cent) of myelogenous leukemia and 11 cases (14.7 per cent) of lymphatic leukemia. In the remaining 5 cases (6.7 per cent) the leukemia was monocytic.

Powell<sup>6</sup> expressed the belief that the higher incidence of acute leukemias reported in recent publications is due to an improvement in diagnosis, especially to recognition of the leukopenic forms of the disease.

That leukemia occurs more frequently in men is generally accepted (Forkner,<sup>1</sup> Powell<sup>6</sup> and others). Our percentage of 69.9 against 30.1, a ratio of 2 males to 1 female, is a further proof. Powell reported the same ratio. In the various types of leukemia this ratio changes. Thus, in our cases we found that for myeloid

TABLE 2—*Age Incidence of Various Types of Leukemia in One Hundred and Twenty-Three Fatal Cases*

Type of Leukemia	Age, Years								Total
	0-10	11-20	21-30	31-40	41-50	51-60	61-70	Over 70	
Stem cell									
Acute	6	3	6	3	1	4			23
Acute aleukemic	1	1	1						3
Chronic aleukemic					2				2
Myelogenous									
Acute	2	3	3	3	3	6	6	2	28
Acute aleukemic				1	1	1	2		5
Chronic			2	6	2	9	1		20
Lymphatic									
Acute	1	2		1	3		3	1	11
Chronic					3	10	7	3	23
Chronic aleukemic	1					2			3
Monocytic									
Acute			1	1	2	1			5
Total	11	9	13	15	17	33	19	6	123

leukemia the ratio was 37 to 16, for lymphatic leukemia 32 to 5 and for stem cell leukemia 24 to 4. Whether the ratios are only incidental or are typical is difficult to decide, as the number of reported cases in the literature is not sufficiently large.

A definitely higher incidence among white persons has been observed and the ratio in our cases was 3 white persons to 1 colored person, or 79 per cent against 28 per cent. We had only 1 Chinese, but the percentage of Chinese patients admitted to the hospital is low.

#### AGE

Table 2 furnishes interesting information regarding the average age of patients with the various forms of leukemia. There was a high percentage of persons with acute leukemia (myelogenous, lymphatic and monocytic) in the older age group, namely, in 22 (29.3 per cent) of the 75 cases of acute leukemia the patients were in the fourth to the sixth decade, in 14 cases (17.3 per cent) the patients were between 61 and 80 years of age and in only 30 cases (40 per cent) were the patients in the first three decades. Only stem cell leukemia showed a marked prevalence in the first to the third decade, namely, 69 per cent and in 7 cases (26.9 per cent) of this type the patients were younger than 10 years. In 24.2 per cent of cases

<sup>6</sup> Powell, W. N. Acute Leukemias, Texas State J. Med. 36:486, 1940.

Also, with Doan and Wiseman,<sup>1a</sup> we recognize the existence of a common ancestor of the myeloid elements, the hemocytoblast, or stem cell, and list, therefore, a fourth type, stem cell leukemia, which is represented in our series by an unusually large number of cases (28, or 22.7 per cent)

Separation of acute from chronic leukemia is difficult in certain borderline cases. However, the acute form presents a fairly characteristic complex group of symptoms, as will be discussed later. The chronic form includes illness in which there is a history of one year's duration from the onset of symptoms, accordingly, we have classified our cases under the terms acute and chronic. In a few cases grouped under chronic leukemia there was an acute exacerbation.

The term aleukemic or subleukemic leukemia, generally used for particular subtypes, seems to be a contradiction in itself. We suggest, therefore, the terms aleukemic myelosis for the myeloid form and aleukemic lymphadenosis for the lymphatic form. These blood dyscrasias manifest themselves mainly in the myeloid

TABLE 1—*Distribution and Classification of One Hundred and Twenty-Three Cases of Fatal Leukemia According to Type of Leukemia and Sex and Race of Patient*

Type of Leukemia	Sex		Race		Total
	Male	Female	White	Colored	
Stem cell					28 (22.7%)
Acute	11	12	15	8	23
Acute aleukemic	1	2	2	1	3
Chronic aleukemic	2		2		2
Myelogenous					53 (43.1%)
Acute	19	9	21	7	25
Acute aleukemic	3	2	4	1	5
Chronic	15	5	16	4	20
Lymphatic					37 (30.8%)
Acute	10	1	10	1	11
Chronic	19	4	20	3	27
Chronic aleukemic	3		3		3
Monocytic					5 (4.1%)
Acute	3	2	3	1	5
				1 (Chinese)	5
Total	86	37	96	27	123
	69.9%	30.1%	78.1%	21.9%	

or the lymphatic organs and not in the peripheral blood and to use any word containing “-emia” seems to be illogical.

For the final classification of a case under a given type of leukemia we used all available clinical data—the peripheral blood picture, results of bone marrow studies and, as the most important aid, the necropsy report. Any case in which autopsy is not done cannot be considered as completely worked up and can be subject to criticism as to its final interpretation and classification.

INCIDENCE

Table 1 shows the distribution of our 123 cases according to type of leukemia, sex and race. One striking figure is the high incidence of stem cell leukemia—namely, 28 cases, or 22.7 per cent. In 26 of these 28 cases, or 92 per cent, the course was fulminant and illness ended fatally within a short time. This is in accordance with the general observation that the younger the patient and the more immature the type cell, the more acute the course. In only 1 case was illness really chronic, lasting six and a half years. In a second case the patient died twelve months after the onset of symptoms. In both cases of chronic illness it was of the aleukemic variety. The ratio between myelogenous, lymphatic and monocytic types is not unusual. We had

quently the initial symptom. General weakness, malaise, easy fatigue and anorexia were mentioned in early stages of acute and of chronic leukemia—in 57.1 per cent of cases of stem cell leukemia, in 15.1 per cent of cases of myelogenous leukemia and in 29.7 per cent of cases of lymphatic leukemia. Acute inflammatory and ulcerative processes in the oral cavity or in the throat were encountered in 20 cases of acute leukemia, mostly of the stem cell and the myelogenous type, and in 7 cases of chronic leukemia. Folkner pointed out that in acute monocytic leukemia these lesions are more severe and consist of deep ulcerations with swelling of the gums and the oral mucosa, while in myelogenous and in lymphatic leukemia the lesions are milder and present only slight inflammation and petechial hemorrhages. Severe bleeding from the nose was also an initial symptom frequently observed, sometimes in association with the lesions in the oral cavity but sometimes as an isolated complaint that induced a patient to seek medical advice. This was noted in 12 cases of stem cell leukemia, in 11 cases of myelogenous leukemia, in 6 cases of lymphatic leukemia and in 1 case of monocytic leukemia.

Spontaneous hemorrhage and hemorrhagic diathesis belong to the syndrome chiefly observed in acute leukemia. Petechial hemorrhages in the skin were encountered only in 1 case of chronic aleukemic lymphadenosis and in 1 case of chronic myelogenous leukemia, while they were noted in 4 cases of acute stem cell leukemia, in 4 cases of acute myelogenous leukemia and in 3 cases of acute lymphatic leukemia. Massive gross hemorrhage may also indicate the hemorrhagic diathesis of the leukemic patient. It was observed twenty-one times in acute myelogenous leukemia and aleukemic myelosis, twelve times in acute stem cell leukemia, seven times in acute lymphatic leukemia, four times in acute monocytic leukemia, three times in chronic myelogenous leukemia and eight times in chronic lymphatic leukemia. Hemorrhages occurred in 73.3 per cent of cases of the acute form and in only 31.2 per cent of cases of the chronic form.

The hemorrhage may manifest itself as bleeding from the nose (32 cases), bleeding of the gums (19 cases), hemoptysis (9 cases), melena (8 cases), menorrhagia (6 cases), conjunctival hemorrhage (5 cases), hematemesis (5 cases), retinal hemorrhage (2 cases) and hematuria (1 case).

This hemorrhagic diathesis is, according to most authors, caused by marked thrombopenia. We encountered a distinct decrease of the blood platelets in 31 cases. Whether vitamin K deficiency is of any etiologic importance has to be studied further. We have found no references to it in the literature.

One of the less frequent symptoms either in the early or in the late stages of the disease is dull or sharp pains. It was observed in 24 cases of acute leukemia and 3 cases of chronic leukemia without any preference for one or the other type. Other symptoms were headaches (7 cases), precordial or sternal pains (5 cases), vague abdominal pains (4 cases), pains in the arms or legs (8 cases) and pains in the gums or cheeks (3 cases). The pain is apparently caused by lesions of the central or the peripheral nervous system. These lesions may consist of hemorrhages or leukemic infiltrations. Tromner and Wohlwill<sup>8</sup> and Schwab and Weiss<sup>9</sup> made extensive studies in this regard and reported frequent involvement of the nervous system.

Difficulties in breathing were observed in 23 cases (10 cases of acute leukemia and 13 cases of chronic leukemia). These symptoms, however, are too vague and too frequently observed in association with other conditions often encountered in

8 Tromner, E., and Wohlwill, F. Ueber Erkrankungen des Nervensystems insbesondere der Hirnnerven bei Leukämie, *Deutsche Ztschr. f. Nervenhe.* **100** 233, 1927. Peripherische Nervenerkrankung bei Leukämie, *Zentralbl. f. inn. Med.* **48** 996, 1927.

9 Schwab, R. S., and Weiss, S. Neurologic Aspects of Leukemia. *Am. J. M. Sc.* **189** 766, 1935.

of myelogenous leukemia the patients were younger than 30 years, while in 21 per cent they were between 31 and 60 years of age and in 30.3 per cent (10 cases) they were between 61 and 80 years of age. The figures for lymphatic leukemia are similar. In 3 cases (27.3 per cent) the patients were in the first three decades, and in 4 cases (36.4 per cent) they were older than 60 years. These figures are important for diagnostic consideration, as they prove that acute leukemia is not all too uncommon in elderly patients. Therefore, if an older patient presents an indefinite clinical picture resembling that of acute leukemia, such as ulcerative lesions in the oral cavity and petechial or gross hemorrhages, the diagnosis of leukemia should be considered and excluded even if the white cell count is low. Differential blood counts and aspirations of bone marrow should be made to rule out this possibility.

The chronic leukemias show a definite prevalence in the middle-aged group. In 34 of 48 cases (70 per cent) the patients were in the fourth to the sixth decade and in 11 cases (22.9 per cent) they were older than 60 years. In only 3 cases (6.3 per cent) were the patients younger than 30 years, and in 1 case of aleukemic lymphatic leukemia the patient was 7 years of age. In 85 per cent of the cases of myelogenous leukemia the patients were between 31 and 60 years of age, while 57 per cent of the cases of lymphatic leukemia represented the same age group.

Summarizing, we find that according to our series, leukemia does not show a definite tendency to occur in young persons, since in the same percentage of cases leukemia occurred in the first three decades and in the fourth and sixth decades. An exception was noted in the case of stem cell leukemia, which occurred chiefly in persons younger than 30 years (93.7 per cent).

#### SYMPTOMATOLOGY

All forms of leukemia present a multitude of symptoms and physical signs and vary so considerably that a physician needs all available laboratory methods to establish firmly a correct diagnosis. It is of more than academic and pathologic interest not only to make a diagnosis of "leukemia" but to determine the type of leukemia. Although a cure for this disease is still not known, the treatment of acute stem cell leukemia is different from that of chronic aleukemic lymphadenosis. There are no pathognomonic symptoms in leukemia, but several symptoms were encountered more frequently in some types than in others. The acute leukemias particularly show certain typical features that are not so frequently seen in the chronic form. We agree with Kaufmann and Loewenstein<sup>7</sup> that it is impossible to correlate clinical observations with a particular cell type.

In our series of cases we have tried to evaluate the clinical features and the results of physical examination and laboratory tests. In several cases it was impossible to obtain a complete history, since many of the patients admitted to the Cook County Hospital are foreign born and frequently were unable to speak and understand English. Many patients had not had previous medical attention and were moribund when admitted, and from them also it was impossible to obtain detailed histories.

The onset in all cases of acute leukemia was abrupt, in cases of chronic leukemia it was insidious. In 3 cases myelogenous leukemia started as chronic leukemia and then suddenly showed the symptoms of the acute form, death occurred after a few weeks. In 12 cases (acute leukemia, 8, chronic leukemia, 4) the disease was first noticed after some trivial minor surgical procedure, such as extraction of a tooth or tonsillectomy. An acute infection of the upper respiratory tract was fre-

<sup>7</sup> Kaufmann, J., and Loewenstein, L. A Study of Acute Leukoses, *Ann Int Med* 12: 903, 1940.

cases the number of the leukocytes was 850 per cubic millimeter. It appears from the literature that acute leukemia may start with a granulopenic blood picture, and it is due to this fact that many instances of acute leukemia have been mistaken for agranulocytosis, even the clinical picture of the latter disease is somewhat similar to that of leukemia. It is, therefore, imperative that blood counts are performed at frequent intervals. In 6 cases (21.4 per cent) of stem cell leukemia the white cell count was below 4,000. Similar low white cell counts occurred in 5 cases of myelogenous leukemia, 6 cases of lymphatic leukemia and 1 case of acute monocytic leukemia. Relatively frequent, however, was an excessively high white cell count. In 32 cases the count was over 200,000 per cubic millimeter, 14 were cases of chronic myelogenous leukemia and 6 cases of acute stem cell leukemia. When comparing counts made at frequent intervals one observes a constant fluctuation, particularly under the influence of treatment and especially after roentgen irradiation of the spleen or bones.

As has been mentioned, the hemorrhagic diathesis in leukemia is caused in many cases by marked thrombopenia. Since platelet counts were not made in all cases, our figures cannot give the true picture in this regard. It is, however, significant that in 31 cases (41.4 per cent) of acute leukemia and in 7 cases (14.6 per cent) of chronic leukemia a marked decline (mostly below 30,000) of the thrombocytes was encountered, while in 73.3 per cent of cases of acute leukemia and in 31 per cent of cases of chronic leukemia spontaneous hemorrhages occurred. One may therefore assume that the actual percentage of cases in which thrombopenia occurs is considerably higher. Like the erythrocytes and the leukocytes, the blood platelets vary in number, as indicated in repeated counts. Minot and Buckman<sup>10</sup> stated that according to their series of 50 cases the number of thrombocytes may be normal, increased or decreased.

In the few instances in which studies of the bleeding and clotting time were made the bleeding time was prolonged in 4 cases of acute stem cell leukemia, in 1 case of acute myelogenous leukemia and in 3 cases of acute aleukemic myelosis, while it was normal in 3 cases of acute stem cell leukemia and in 1 case of acute aleukemic myelosis. The clotting time was prolonged in 2 cases of acute stem cell leukemia and in 1 case of acute lymphatic leukemia and was within normal range in 1 case of acute stem cell leukemia, in 1 case of acute myelogenous leukemia and in 3 cases of acute aleukemic myelosis. Forkner mentioned only briefly that the coagulation time in cases of acute leukemia may be prolonged.

Considerable work has been done on the influence of leukemia on the basal metabolic rate. As early as 1869 Voit and Pettenkofer observed a marked elevation of the basal metabolic rate in a case of leukemia. Later their observation was confirmed by many authors (Minot and Means,<sup>11</sup> Gunderson,<sup>12</sup> Riddle and Sturgis,<sup>13</sup> and others). Krantz and Riddle<sup>14</sup> and Lennox and Means<sup>15</sup> have expressed the

10 Minot, G. R., and Buckman, T. E. The Blood Platelets in Leukemias, *Am J M Sc* **169** 477, 1925.

11 Minot, G. R., and Means, J. H. Metabolism—Pulse Ratio in Exophthalmic Goiter and in Leukemia with Remarks to Similarities in the Symptomatology of These Diseases. *Arch Int Med* **33** 576 (May) 1924.

12 Gunderson, A. H. The Basal Metabolism in Myelogenous Leukemia and Its Relation to the Blood Findings, *Boston M & S J* **185** 785, 1921.

13 Riddle, M. C., and Sturgis, C. C. Basal Metabolism in Chronic Myelogenous Leukemia, *Arch Int Med* **39** 255 (Feb) 1927.

14 Krantz, C. Q., and Riddle, M. C. The Basal Metabolism in Chronic Lymphatic Leukemia, *Am J M Sc* **175** 229, 1928.

15 Lennox, W. G., and Means, J. H. Study of Basal and Nitrogenous Metabolism in a Case of Acute Leukemia During Roentgen-Ray Treatment. *Arch Int Med* **32** 705 (Nov) 1923.

leukemic patients, i e, bronchopneumonia, pulmonary tuberculosis and cardiac decompensation, to be of any diagnostic value

The main and most constant abnormality revealed on physical examination was enlargement of the liver, the spleen and the lymph nodes Table 3 gives a summary of the weights of the liver and the spleen in our cases The lymph nodes most frequently enlarged were the cervical group Enlargement of the lymph nodes was the outstanding feature in lymphatic and in stem cell leukemia, while enlargement of the liver and the spleen was more common in the myelogenous type However, to a lesser degree and less frequently the lymph nodes are enlarged in myelogenous leukemia, and still less frequently enlargement of the spleen and the liver is observed in lymphatic leukemia

LABORATORY DATA

The diagnosis of leukemia, as a rule, is definitely established by a blood and a bone marrow smear As we did not determine the bone marrow picture for all

TABLE 3—*Weight of the Liver and the Spleen in One Hundred and Twenty-One Cases of Fatal Leukemia\**

Type of Leukemia	Liver, Gm				Spleen, Gm			
	Average Weight	Under 1,500	1,500 to 2,500	Over 2,500	Average Weight	Under 150	150 to 300	Over 300
Stem cell								
Acute	1,760	8	9	4	670	5	4	15
Acute aleukemic	1,830	1	1	1	510		1	2
Chronic aleukemic	3,145		1	1	993			2
Lymphatic								
Acute	2,230	2	6	4	655		5	7
Chronic	2,340	2	10	7	950	2	1	16
Aleukemic	2,080	1	1	1	560		1	2
Myelogenous								
Acute	1,950	4	18	4	540	5	4	18
Chronic	2,890	1	7	1	1,530	1		18
Aleukemic	1,750		1	1	790			5
Monocytic								
Acute	1,945	1	4		335		3	2
No of Cases	105	20	61	24	121	13	21	87
Total								

\* Note that the largest livers and spleens occurred in cases of chronic myelogenous leukemia

patients while they were alive but did in the majority of cases at autopsy, we shall discuss later the differential counts of the peripheral blood and the bone marrow and their relation together with the other autopsy observations

One of the most common complications of leukemia is marked anemia It was encountered in 103 (83.7 per cent) of our 123 cases In 63 cases (51.2 per cent) the hemoglobin concentration was under 50 per cent Comparable figures were obtained with the count of the red blood cells In 70 cases (56.9 per cent) the count was below 2,500,000 In most cases the anemia was of the hypochromic type Comparing the figures for the various types of leukemia, we found a hemoglobin concentration below 70 per cent in 64 cases (85.3 per cent) of acute leukemia and in 29 cases (60.4 per cent) of chronic leukemia It was below this percentage in 27 (96.4 per cent) of 28 cases of stem cell leukemia, 36 cases (67.9 per cent) of myelogenous leukemia, 25 cases (67.5 per cent) of lymphatic leukemia and 5 cases (100 per cent) of monocytic leukemia

It is a well known fact that in leukemia the total white cell count is not always markedly elevated This holds true especially for aleukemic or subleukemic groups, but it is not infrequently observed that the white cell count is considerably below the normal range, especially in the initial or terminal stages of the disease In some

## DIAGNOSIS

Of 112 cases of our series in which a definite clinical impression was recorded, the diagnosis of leukemia was correct in 87, or 77.7 per cent. Cases in which a clinical diagnosis of one type of leukemia was made and autopsy revealed another type were counted as instances of correct diagnosis, but when the clinical impression was "blood dyscrasia" without further specification, it was not considered a correct diagnosis.

A few wrong clinical diagnoses may be mentioned: lobar pneumonia or bronchopneumonia, 3 cases, Vincent's angina, 1 case, chronic aleukemic stem cell leukemia mistaken for Hodgkin's disease, 1 case, and rheumatic heart disease, sepsis caused by *Streptococcus viridans* or arteriosclerotic heart disease, 7 cases. A malignant growth in the gastrointestinal tract or a bleeding peptic ulcer was suspected in 2 cases of acute myelogenous leukemia and a mediastinal tumor in 1 case of acute stem cell leukemia. A diagnosis of splenomegaly was made in 1 case of acute aleukemic myelosis. In 2 cases chronic lymphatic leukemia was discovered incidentally at autopsy.

It is not our purpose to discuss in detail the differential diagnosis of leukemia. It may suffice to mention that the so-called "leukemoid reactions" have to be clearly differentiated from true leukemia. A blood picture simulating that of leukemia may be observed in association with pertussis, infectious mononucleosis, tuberculosis, Vincent's angina and any other infectious disease. Neoplasms, such as carcinoma and melanoma, may present a similar picture. Much more difficult at times is the demarcation of leukemia from lymphosarcoma and Hodgkin's disease.

## ANATOMIC OBSERVATIONS

In reviewing the necropsy reports here we shall be particularly concerned with the organs of the hemopoietic system, i. e., the liver, the spleen and the bone marrow. In a number of our cases in which the clinical diagnosis was vague or incorrect the true condition was determined after autopsy. The pathologic changes in the spleen, the liver and the bone marrow were characteristic of leukemia.

In table 3 are given the weights of the liver and the spleen in all cases in which they were recorded. In 105 cases the weight of the liver was mentioned, while in 121 cases the weight of the spleen was noted. The liver was usually large and the highest weights were noted in the cases of chronic myelogenous leukemia. This also held true for the size of the spleen. However, the size and the weight of the liver and the spleen are not diagnostic criteria in differentiating the type of leukemia, as seen from our statistics. The largest liver in our series weighed 5,535 Gm and occurred in a patient with chronic myelogenous leukemia. The largest spleen occurred in a patient with chronic lymphatic leukemia, and its weight was 2,865 Gm.

The microscopic appearance of the liver in all types of leukemia is characteristic. The liver may show leukemic cells either within the dilated sinusoids or within the periportal fields. In only about 50 per cent of cases the connective tissue of Glisson's capsule shows a marked infiltration with mature and immature lymphocytes or myeloid cells. According to Jaffé<sup>23</sup> a typical feature of monocytic leukemia is the presence within Kupffer's cells of granules which yield a positive oxidase reaction. This statement was borne out in 3 of our 5 cases of monocytic leukemia, but such granules were occasionally observed in cases of myelogenous leukemia. The type cell of myelogenous leukemia found in the liver is the myeloid cells in all stages of development. In the acute forms mainly the blast cells were

23 Jaffé, R. H. Personal communication to the authors. 1937.



belief that the basal metabolic rate is of prognostic value and an indicator of the severity of the leukemic process. A sudden sharp rise in the basal metabolic rate is a sign of bad prognosis. There are cases in which the basal metabolic rate is 100 per cent above normal. To what extent this increase is actually caused by the leukemic process is difficult to evaluate, since accompanying hyperthyroidism is observed in cases of leukemia. Of 11 cases in which the basal metabolic rate was determined, there was an elevation over 10 per cent in 10 and in 1 it was within normal limits.

Of some value is determination of the urea nitrogen and the nonprotein nitrogen in the blood of leukemic patients. Becher and Herrmann<sup>16</sup> reported that these substances were elevated. Of the 20 cases in which determinations were made, the level of nonprotein nitrogen was normal in 9 and considerably elevated in 11.

The uric acid content of the blood was increased in 5 cases.

The cholesterol content of the blood was normal in 3 cases and was increased in 1 case. Mueller<sup>17</sup> reported subnormal values in 3 cases of lymphatic leukemia and 13 cases of myelogenous leukemia.

Before concluding the discussion of the symptomatology of leukemia a few symptoms which were less frequently observed and which are referable to the leukemic process are worth mentioning. Occasionally, patients complain of edema of the extremities, which could be verified on physical examination. Those cases in which the edema is caused by a cardiorenal pathologic condition should be excluded as possible instances of leukemia. Edema in cases of leukemia could be explained by encroachment of the enlarged lymph nodes on the large vessels in the groin or by obliteration of the lymphatics by the leukemic tissue within the nodes. As will be shown later, frequently the entire normal architecture of the lymph node is destroyed and replaced by pathologic cells and tissue. No lymph sinuses were recognizable. We encountered this symptom in 8 cases of myelogenous leukemia, in 2 cases of stem cell leukemia and in 2 cases of lymphatic leukemia.

Vertigo, observed not infrequently in leukemia, is caused by infiltration of leukemic tissue into the internal ear. Gottstein<sup>18</sup> and Politzer<sup>19</sup> reported cases in which leukemia simulated Ménière's syndrome. We encountered the symptom of vertigo in 9 cases.

In textbooks great importance is attributed to the occurrence of priapism in leukemia. We encountered the symptom in only 1 case of acute myelogenous leukemia. Craver<sup>20</sup> encountered it only once in his series of more than 100 cases and Barney, Hunter and Mintz<sup>21</sup> once in 51 cases. Warthin,<sup>22</sup> however, reported the occurrence of priapism in one fourth of his cases.

16 Becher, E., and Herrmann, E. Das Zustandekommen der hohen Werte des gebundenen und freien Aminostickstoffes im enteiserten Blute bei Leukämien, München med Wchnschr **73** 1312, 1926.

17 Mueller, G. L. The Cholesterol Metabolism in Health and in Anemia, Medicine **9** 130, 1930.

18 Gottstein, J. Ueber den Meniere'schen Symptomen-complex, Ztschr f Ohrenh **9** 37, 1880.

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*Bone Marrow*—Most important of all is examination of the bone marrow. It reveals best the true picture of the disease, and by comparing its cells with those of the peripheral blood one can often reconstruct and follow the course of a leukemic disorder. The reports in the literature and the experience of hematologists indicate how the blood picture may change considerably during the course of the disease. It is, therefore, of the utmost importance to follow these changes by repeatedly making blood counts, smears and sternal punctures in order to obtain the true picture.

In the following paragraphs we shall give a brief summary of the bone marrow studies as compared with the peripheral blood picture in our series of cases. Most of the bone marrow counts were made on marrow obtained from the femur at autopsy.

*Acute Stem Cell Leukemia* Smears of bone marrow and of blood were studied in 23 cases. In 15 cases a differential count of the bone marrow was made. In all but 4 cases the marrow was described as hyperplastic and very cellular. In 4 cases the marrow was fatty. In 17 cases (74 per cent) the majority of cells were stem cells. In 6 cases the percentage of stem cells in the marrow corresponded roughly to that in the peripheral blood. In 11 cases the predominant cell in the marrow was the stem cell, in 7 of these 11 cases the peripheral blood showed a further maturation of the cells in the direction of the lymphoblast, while in 4 cases the type cells in the peripheral blood were myeloblasts or myelocytes.

In 4 cases the bone marrow contained only a moderate number of stem cells, while lymphoid or myeloid cells dominated the picture, the peripheral blood, however, showed a higher percentage of stem cells than the marrow, indicating a dedifferentiation of cells. In 1 case transitional forms between stem cells and myeloblasts were the outstanding cell type in the marrow, while the blood smear showed 56 to 94 per cent stem cells. These figures represent average values obtained from repeated counts. In all forms of leukemia three trends of development are recognizable: a gradually increasing output of mature cells, an increased number of immature cells in the marrow and the peripheral blood and an irregular fluctuation of the circulating cells.

The bone marrow, and to a lesser degree the peripheral blood, show a large variety of cell types in stem cell leukemia, in contrast to the number in lymphatic leukemia. All stages of erythropoiesis, myelopoiesis and lymphopoiesis can be seen, but the type cell remains the undifferentiated stem cell or hemocytoblast. Numerous mitotic figures can be seen.

*Acute and Chronic Aleukemic Stem Cell Leukemia* Five cases were studied. In only 1 case was the marrow fatty, in the other 4 cases it was hyperplastic and very cellular. In all cases the stem cells formed 40 to 80 per cent of the marrow cells, a large percentage of erythroblasts was also seen but only an occasional immature myeloid or lymphoid cell. The peripheral blood showed no appreciable abnormalities, in only 2 cases moderate relative lymphocytosis was observed.

*Acute Myelogenous Leukemia* Twenty-three cases were studied, in 1 case only was the bone marrow available, while in 4 cases the bone marrow was described as fatty and containing only a small number of myelocytes or myeloblasts. The peripheral blood in these 4 cases showed a corresponding number of these cells. In the remaining cases cells in all stages of myelopoiesis could be seen, in some the blast forms were predominant, and in others the more mature forms such as myelocytes or juvenile granulocytes, predominated. In most cases the differential count of the marrow corresponded approximately to that of the peripheral blood. The percentage of erythroblasts or megaloblasts varied from 1 to 20. However, in 1 case 95 per cent of the marrow cells were erythroblasts while in the

observed, which frequently gave a negative oxidase reaction. The microscopic picture of the liver in the so-called "aleukemic" forms did not differ from that in the fully developed leukemias. The spleen was similar in this respect. Occasionally, an increased amount of hemosiderin pigment was seen in the liver.

The microscopic appearance of the spleen is characteristic. In almost all cases of myelogenous leukemia the spleen shows the so-called "myeloid metaplasia." The normal architecture is completely replaced by myeloid tissue showing mainly immature myeloid cells. In the acute forms, the early cell types, that is, the myeloblasts, are predominant, and mitotic figures are prominent. The oxidase reaction in many cells is negative. In the chronic forms, the more mature cells dominate the picture, myelocytes and mature granulocytes are the most common cells and the oxidase reaction is positive. Occasionally, eosinophilic myelocytes and granulocytes are seen in increased number. Not infrequently marked hemosiderosis is noted, indicating an increased destruction of erythrocytes. Important is the fact that the structures of the spleen and the liver in aleukemic myelosis do not differ from those in leukemias in which the peripheral blood shows all immature forms.

In stem cell leukemia the type cell is displayed predominantly in the spleen, but besides this cell frequently myeloid or immature lymphoid cells can be found. As in myeloid leukemia, erythroblasts and normoblasts are among the cells constituting the myeloid metaplasia.

In all forms of lymphatic leukemia the spleen presents a monotonous and uniform picture. Again, the normal architecture is completely obliterated, and one sees a uniform mass of lymphoid cells, mostly lymphocytes and lymphoblasts. The oxidase reaction is negative. In only a few cases can marked siderosis be observed.

In the few cases of monocytic leukemia studied monocytes and monoblasts dominated the picture.

*Lymph Nodes*—The lymph nodes were frequently involved. Acute stem cell leukemia produced the most marked enlargement of almost all the groups of regional lymph nodes. The mesenteric and other abdominal nodes were most frequently involved in all types of leukemia. The inguinal, cervical and axillary nodes were less frequently enlarged.

The microscopic appearance of the lymph nodes varies, naturally, in the different types of leukemia. A monotonous picture is seen in all cases of lymphatic leukemia, in which the nodes are transformed into a uniform mass of lymphocytes and lymphoblasts. There is no recognizable suggestion of any normal architecture. In myelogenous leukemia one sees "myelogenous metaplasia" similar to that observed in the spleen and the liver. All forms of mature and immature myeloid cells can be observed. Only remnants, if any, of the former structures are left. Immature red blood cells are present. In stem cell leukemia the type cell replacing the lymphoid tissue is the stem cell, which gives a negative oxidase reaction. Frequently also, immature lymphoid or myeloid cells constitute the "leukemic tissue." Monocytic cells were mostly seen in acute monocytic leukemia. In 18 cases (stem cell leukemia, 5, myelogenous leukemia, 4, and lymphatic leukemia, 9) a diffuse infiltration of the leukemic cells into the capsule of the lymph node and into the perinodular tissue was noticed. This observation may be relevant in the consideration of the nature of the leukemic process as an infiltrating growth, a feature usually considered as a criterion of a malignant tumor. This supports the theory that leukemia is a neoplastic disease. In 1 of our cases there was a definite malignant degeneration of a group of mediastinal lymph nodes into a lymphosarcoma with multiple metastases.

cases the peripheral blood showed predominantly lymphocytes and lymphoblasts. In 1 case repeated blood smears showed a gradual decrease of the granulocytes from 80 to 6 per cent, while the lymphoid cells rose in the same time from 15 to 92 per cent.

**Chronic Aleukemic Lymphadenosis** In 1 case the bone marrow was fatty, and in another case it was very cellular and hyperplastic. The first case is not remarkable, as the bone marrow showed lymphocytes and lymphoblasts and only a few myeloid cells. The peripheral blood, however, had 47 per cent granulocytes and 49 per cent lymphoid cells.

**Acute Monocytic Leukemia** All 5 cases were studied completely. The marrow was hyperplastic and contained 70 to 96 per cent monocytoïd cells (monocytes and monoblasts). Besides these cells, however, mature and immature myeloid cells and erythroblasts could be seen in varying numbers. The lymphocytes were less prominent, not more than 7 per cent. With the exception of 1 case the percentage of the monocytes was less in the blood than in the marrow. In this case a large number of monoblasts (up to 32 per cent) were present in the peripheral circulation. One case is remarkable in that the marrow contained 96 per cent monocytoïd cells and only 0.4 per cent myelocytes, while the blood smear showed 90 per cent myeloblasts. In another case, the percentage of monoblasts rose gradually from 0 to 7 to 32, while the corresponding percentages for the monocytes were 25, 68 and 25. In all but 1 case the peripheral blood contained monocytes and monoblasts, in 2 cases the immature cells outnumbered the mature monocytes.

#### LEUKEMIC INFILTRATIONS

Accumulation of immature white corpuscles is not limited to the hemopoietic organs. We encountered the so-called "leukemic infiltrations" in almost all organs and tissues of the body. There is apparently no particular recognizable preference of one cell type for any special organ or organ system. The most frequently involved organ in all forms of leukemia is the kidney (in 78 cases, or 63 per cent). The myeloid or lymphoid cells are found within the glomerular tufts or in the interstitial connective tissue. In 5 cases the renal capsule and the perirenal fatty tissue also showed marked infiltration with leukemic cells.

The heart was involved in 43 cases (34 per cent). Here the cells were encountered within the capillaries and in the interstitial tissue between the myocardial fibers. While the infiltration of the kidney was evenly distributed among the various forms of leukemia, we encountered the highest percentage of cardiac involvement in acute stem cell leukemia, in 14 cases (54 per cent) the heart showed marked infiltration with stem cells. The heart was involved in 54 per cent of cases of acute lymphatic leukemia. In all the other forms an infiltration of the heart was not present in more than 25 per cent of cases.

The intestines showed leukemic infiltrations in 17 cases (13 per cent). Among the other organs or structures which were less frequently infiltrated with immature white cells we mention in the order of frequency only the lungs (16 cases), adrenals (14 cases), thymus (12 cases), pancreas (9 cases), central nervous system (8 cases), skin (5 cases), oral cavity (5 cases), genitalia (5 cases), thyroid (2 cases), ribs (2 cases) and urinary bladder (1 case). The infiltrations in the skin and the central nervous system are important from the clinical standpoint as they may cause severe symptoms, in the skin they appear as diffusely distributed nodules, while in the central nervous system they may give rise to such symptoms of irritation or paralysis as headaches, convulsions, vertigo, blindness, deafness or paralysis of the extremities.

peripheral blood 97 per cent of the white cells were myeloblasts, 1 per cent were neutrophilic granulocytes and 2 per cent were lymphocytes. In another case there was marked eosinophilic granulopoiesis, 60 per cent of all the marrow cells being eosinophilic myelocytes, 11.4 per cent myeloblasts and 1.6 per cent neutrophilic granulocytes. The smear of peripheral blood in this case consisted of 32 per cent eosinophilic granulocytes, 50 per cent myeloblasts, 10.5 per cent polymorphonuclear granulocytes, 2 per cent neutrophilic promyelocytes, 3.5 per cent mature eosinophilic granulocytes and 5.5 per cent lymphocytes. In most cases the bone marrow contained more blast forms than did the peripheral blood.

**Acute Aleukemic Myelosis.** Five cases could be studied, but in 1 case a blood smear was not available. In the other 4 cases the bone marrow was very cellular and hyperplastic and contained immature myeloid cells, mainly neutrophilic myelocytes and erythroblasts. Mature granulocytes, plasma cells and lymphocytes were only occasionally observed. The blood smear in those cases in which it was available showed marked granulopenia (6 per cent of cells) but contained 16 per cent erythroblasts, 24 per cent monocytes, 50 per cent lymphocytes and 4 per cent "irritation forms." In 2 other cases it showed up to 6 per cent myelocytes and 2 per cent myeloblasts.

**Chronic Myelogenous Leukemia.** In all 17 cases studied the bone marrow was hyperplastic and very cellular. The differential counts of the marrow resembled each other considerably. Cells of all stages of myelopoiesis and erythropoiesis were seen, predominantly neutrophilic myelocytes, promyelocytes and metamyelocytes. Occasionally, monocytoïd cells were observed. The peripheral blood resembled the marrow in its constituents. However, in 1 case the marrow contained 17 per cent myeloblasts, 12.6 per cent promyelocytes and 1.6 per cent metamyelocytes, while the blood smear showed 24 per cent myeloblasts, 9.4 per cent promyelocytes and 27 per cent metamyelocytes. In another case 65.1 per cent myeloblasts were counted in the marrow, but the peripheral blood smear showed 8 per cent myeloblasts and at a second count 5.4 per cent myeloblasts and only 20 per cent myelocytes. A third case is worth mentioning, because the marrow showed nothing remarkable except 0.3 per cent myeloblasts but the blood smear showed 13.6 per cent myeloblasts.

**Chronic Myelogenous Leukemia with Acute Exacerbation.** The marrow in the 3 cases studied did not present any remarkable features different from the marrow in other cases of myelogenous leukemia. It is important, however, to note that in 2 cases during the chronic phase the peripheral blood contained mainly myelocytes and only 1 per cent myeloblasts, while in the terminal acute phase the percentage of myeloblasts rose to 81 and 95, respectively, the highest count for myeloblasts in our series.

**Acute Lymphatic Leukemia.** As do all the other organs, the bone marrow presents a monotonous picture in all forms of lymphatic leukemia. In 7 of the 11 cases in our series the bone marrow was hyperplastic and cellular. It consisted almost exclusively of lymphocytes or lymphoblasts (81 to 95 per cent) in almost all cases. The balance of the marrow cells were mature and immature myeloid cells, erythrocytes and erythroblasts. The blood smear presented a similar picture. On repeated blood counts distribution of the cells varied only slightly.

**Chronic Lymphatic Leukemia.** Only 15 of 23 cases could be studied completely. The bone marrow was hyperplastic in 13 cases and fatty in 4. The picture was the same as that described for acute lymphatic leukemia. The majority of the marrow cells were mature or immature lymphoid cells (80 to 95 per cent). Only in 4 cases were active myelopoiesis and erythropoiesis seen. But even in those

## TREATMENT

Since leukemia is a hopeless and incurable disease, we need to say only a few words about treatment. The most widely used therapeutic measure, according to the literature and in our series of cases, was repeated transfusion of blood. Transfusions were given in all stages and types of leukemia, and frequently a favorable temporary response could be noticed. The treatment of second choice is roentgen or radium irradiation of the spleen, the mediastinal region, long and short bones and enlarged lymph nodes. Total irradiation of the whole body was employed. While the transfusions never had any untoward effect, exacerbation of symptoms and a rapid downhill course of the patient were frequently observed after irradiation in cases of acute leukemia, without any reference to the type of leukemia. This is in accordance with the reports in the literature. Forkner,<sup>1</sup> Stengel and Pancoast<sup>24</sup> and Minot and Isaacs<sup>25</sup> expressed the opinion that roentgen ray treatments were contraindicated in case of acute leukemia. Naturally, severe anemia, leukopenia, thrombopenia and a too rapid decrease of the myeloid elements would indicate a discontinuation of irradiation in any type of leukemia. An increased output of immature cells, especially of the blast type, denotes a harmful effect of irradiation.

Arsenicals were administered in several cases but without any demonstrable value.

Transfusions of bone marrow and therapy with sulfonamide compounds have proved of no avail.

## SUMMARY

One hundred and twenty-three cases of leukemia are reviewed. This represents 0.86 per cent of 14,400 consecutive cases in which autopsy was performed at the Cook County Hospital from 1929 to March 1941.

These cases are classified in three ways: (*a*) according to the clinical course, as acute leukemia or chronic leukemia, (*b*) according to the type cell in the peripheral blood, bone marrow and tissues, as stem cell leukemia (28 cases), myelogenous leukemia (53 cases), lymphatic leukemia (37 cases) and monocytic leukemia (5 cases), and (*c*) as leukemic or aleukemic disease. The frequent occurrence (22 per cent) of stem cell leukemia is noted.

The incidence of leukemia with regard to race, sex and age is tabulated and discussed. In our cases 69.9 per cent of the patients were male, 30.1 per cent were female, 78 per cent were white and 22 per cent were colored. The high incidence of acute leukemia in the older age groups is unusual. Stem cell leukemias occurred most frequently in persons in the first three decades.

The symptomatology of leukemic disease is reviewed, and the relative frequency of the symptoms commonly observed in various forms of leukemia is discussed. Previous observations by other authors that acute leukemia of all types presents a typical and almost pathognomonic syndrome can be corroborated.

Enlargement of the liver and the spleen was most commonly encountered in myelogenous leukemia and less frequently in lymphatic leukemia. Generalized lymphadenopathy was the outstanding abnormality in lymphatic leukemia and stem cell leukemia.

Marked anemia was observed in all forms of leukemia.

24 Stengel, A., and Pancoast, H. K. The Treatment of Leukemia and Pseudoleukemia with X-Ray, *J. A. M. A.* **59** 1166 (Sept. 28) 1912.

25 Minot, G. R., and Isaacs, R. Lymphatic Leukemia, Age Incidence, Duration and Benefit Derived from Irradiation, *Boston M. & S. J.* **191** 1, 1924.

On the other hand, from the pathophysiologic standpoint it is important to note that the organism reacts even in leukemia as in an infection, with the output of mature polymorphonuclear leukocytes, although an abundant number of immature white cells are present in the blood and in the tissues. The exudate in pneumonia and the pus in phlegmons or abscesses consists chiefly of mature polymorphonuclear leukocytes. In a case of chronic lymphatic leukemia a phlegmon of the buttocks and a septic infarct in the lung consisted of normal pus cells, an abscess of the lung in a case of stem cell leukemia contained only a small number of stem cells, and in a case of chronic myelogenous leukemia the base of an extensive erosion of the cervix was diffusely infiltrated by lymphocytes.

Apparently, the immature white cells have no phagocytic power, and to combat the invading lymphocytes the organism sends out the regular troops, the pus cells, as in the case of any infectious disease.

#### HEMORRHAGES

Petechial or massive hemorrhages were one of the common clinical symptoms of all types of leukemia, occurring mainly, however, in the acute forms. The autopsy reports show that the hemorrhages may be more extensive and may involve more organs than physical examination can reveal. The most widespread and extensive hemorrhages were encountered in cases of acute stem cell leukemia and acute myelogenous leukemia. The most frequently involved organs were the skin, the gastrointestinal tract, the epicardium, the endocardium, the conjunctivas and the pleuras.

#### ASSOCIATED DISEASES

In reviewing our cases of leukemia we were interested in the associated diseases discovered incidentally at necropsy. The diseases encountered are no doubt coincidental and have no relation to leukemia.

The complication most frequently encountered (forty-four times) was bronchopneumonia and lobar pneumonia, in 14 cases of chronic lymphatic leukemia alone pneumonia was the cause of death. Remarkable was the frequent incidence of hyperthyroidism and nodular goiters in association with all forms of leukemia. We encountered it in 18 cases (14.6 per cent). We have already discussed the elevation of the basal metabolic rate and could not confirm reports found in the literature that the basal metabolic rate of patients with leukemia is generally elevated.

The finding of tuberculosis in 16 cases or 13 per cent, is not unusual, since the general autopsy material in the Cook County Hospital shows a high incidence of tuberculosis. The occurrence of hydrothorax in 13 cases, ascites in 10 cases and hydropericardium in 8 cases is also not particularly high. These transudates apparently do not represent the expression of a separate disease but are symptoms of the leukemic process and of a disturbance of the circulation of lymph or blood. The enlarged lymph nodes often compress blood or lymph vessels, causing congestion and transudation in the dependent regions.

Ulcerative proctitis and colitis were encountered in 7 cases, all acute stem cell leukemia. Ulcerative processes in the oral cavity were not uncommon in the acute phase. Numerically much less prominent but important for the concept of the disease was the association of other malignant conditions of the hemopoietic system. We observed 1 case of multiple myeloma and 1 case of myelosarcoma in association with chronic lymphatic leukemia and with acute myelogenous leukemia, respectively.

# CLINICAL OBSERVATIONS ON OSTEOPETROSIS AND MYELOFIBROSIS

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There is considerable interest in clinical conditions resembling leukemia or refractory anemia, in which investigation of the bone marrow reveals fibrosis or considerable diminution of the cellular elements. Until recently such conditions were properly identified only at postmortem examination, but at present the frequent use of sternal puncture or biopsy has made it possible to diagnose the condition during life at various stages of its development. According to our clinical observations, the results of microscopic studies on sternal bone and marrow obtained by biopsy and roentgen ray observations, two main disease entities are encountered. These are (1) osteopetrosis (Albers-Schonberg disease, or marble bone disease) and (2) myelofibrosis (myelosclerosis, leukoerythroblastic anemia, myelophthisic anemia, osteosclerotic anemia or nonleukemic myelosis). It is the purpose of this communication to report a case of osteopetrosis and 17 cases of myelofibrosis, in all except 4 of which the diagnosis was made during life.

The disease process known as osteopetrosis (a term suggested by Karshner<sup>1</sup> in 1926 and meaning "stony bone") was first described by Albers-Schonberg<sup>2</sup> in 1904, and since then about 125 cases have been reported.<sup>3</sup> The diagnosis can be made specifically by roentgenograms. The entire osseous system is markedly and usually uniformly dense to roentgen rays (fig 1). The periosteum as discerned in roentgenograms is intact, but transverse striations of different degrees of density and multiple fracture sites are frequently observed in the shafts of the bones. The generalized condensation of bone found in osteopetrosis cannot be confused with the isolated or scattered condensations of bone present in such conditions as osteopoikilosis,<sup>4</sup> condensing osteitis, eburnizing osteitis, melorheos-

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1 Karshner, R G. Osteopetrosis, *Am J Roentgenol* **16** 405, 1926

2 Albers-Schonberg, H E. Rontgenbilder einer seltenen Knochenerkrankung, *Munchen med Wchnschr* **51** 365, 1904

3 (a) Clifton, W M, Frank, A, and Freeman, S. Osteopetrosis (Marble Bones), *Am J Dis Child* **56** 1020 (Nov) 1938. (b) Fairbank, H A. Increased and Decreased Density of Bone with Special Reference to Fibrosis of the Marrow, *Brit J Surg* **1** 27, 1939. (c) Karshner<sup>1</sup>. (d) Kramer, B, and Halpert, B. Marble Bones. I Clinicopathological Observations, *Am J Dis Child* **57** 795 (April) 1939. (e) Kramer, B, Yuska, H, and Steiner, M. Marble Bones. II Chemical Analysis of Bone, *ibid* **57** 1044 (May) 1939. (f) Lamb, F H, and Jackson, R L. Osteopetrosis (Marble Bone Disease), *Am J Clin Path* **8** 255, 1938. (g) McCune, D J, and Bradley, C. Osteopetrosis (Marble Bones) in an Infant, *Am J Dis Child* **48** 949 (Nov) 1934. (h) McPeak, C N. Osteopetrosis. Report of Eight Cases Occurring in Three Generations of One Family, *Am J Roentgenol* **36** 816, 1936. (i) Nussey, A M. Osteopetrosis, *Arch Dis Childhood* **13** 161, 1938. (j) Wolf, C. Ueber einen Fall von osteosklerotischer Pseudoleukämie. Beitrag zur Frage der Osteosklerosen, *Beitr z path Anat u z allg Path* **89** 151, 1932.

4 Hollv, L E. Osteopoikilosis. Five Year Study, *Am J Roentgenol* **36** 512, 1936



The white blood cell picture showed considerable variability and fluctuation. Attention is drawn to the observation that marked leukopenia may be observed in the early or the late stages of stem cell leukemia and myelogenous leukemia, especially in the acute forms. Marked thrombopenia may cause a hemorrhagic diathesis.

The typical microscopic picture of the liver, the spleen and the lymph nodes is described. "Myeloid metaplasia" was frequently noted in myelogenous leukemia and stem cell leukemia.

Differential counts of bone marrow are compared with those of peripheral blood. The importance of repeated counts is stressed.

The incidence and the distribution of petechial and massive hemorrhages are discussed.

Repeated transfusions of blood were the most beneficial treatment in our cases but gave only temporary relief.

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periosteum. Scattered and even fairly widespread fibrosis of the marrow may be an associated finding in many disorders, such as atypical Paget's disease,<sup>13</sup> neoplastic osteal processes, bony metastases of prostatic carcinoma,<sup>14</sup> myeloma,<sup>15</sup> septicemia,<sup>9</sup> benzene poisoning and radiation poisoning.<sup>16</sup> The fibrotic changes in myelofibrosis may, however, be primary and recognized during life.

Myelofibrosis is clinically characterized by weakness, dyspnea, refractory anemia, splenomegaly, periostitis and bone pains which frequently are "deep seated" (in the back and lower extremities). It occurs equally often in the two sexes and may be evident at birth or in late adult life. There are no familial or hereditary characteristics known. The prognosis for survival varies from five to six weeks when the disease is acute to several years when it is chronic. The causation is unknown.

The cellular changes of the peripheral blood of patients with myelofibrosis and those with osteopetrosis are frequently similar. The peripheral blood picture resembles occasionally that of chronic myeloid leukemia, but more often that of a refractory type of anemia associated with leukopenia, thrombopenia and the presence of a few immature erythroid and myeloid cells. Various workers<sup>17</sup> have described the same hematologic picture in patients with carcinomatosis, myelomatosis, "spent" polycythemia and megakaryocytic hepatosplenomegaly. The end stage of polycythemia resembles that of the primary disease, whereas megakaryocytic hepatosplenomegaly associated with more or less myelofibrosis may be an early stage or a late stage of the condition. The disease must be differentiated from leukemia, aplastic anemia, Gaucher's disease, Banti's disease, myeloma, osteitis fibrosis cystica, syphilis, skeletal metastases (especially carcinoma of the prostate), osteoplastic cancer, osteomyelitis, radiation osteitis, sclerosis of phosphorus or fluorine poisoning, periosteitis, malaria, Hodgkin's disease and amyloid disease.

The postmortem observations are usually hepatosplenomegaly and occasionally generalized lymphadenopathy, a sclerotic or fibrotic marrow and sclerosis or rarefaction of the osseous system. Microscopically, the spleen, liver and lymph nodes often show chronic inflammatory changes with fibrosis, myeloid hyperplasia and extramedullary erythropoiesis. The marrow cavity may be filled diffusely with fibrous tissue, or there may be areas of hemopoietic tissue interspersed in the fibrous tissue. The endosteal bony trabeculations are usually increased in size and number.

The disease in the cases reported in this communication was identified mainly during life (except in cases 5, 6, 14 and 15) and presented the following clinical classifications:

- 1 Osteopetrosis (Albers-Schonberg, or marble bone, disease)
- 2 Myelofibrosis (myelosclerosis, leukoerythroblastic anemia, osteosclerotic anemia)

13 Jaffe, H. L. Atypical Form of Paget's Disease Appearing as Generalized Osteosclerosis, *Arch Path* **16** 769 (Dec) 1933.

14 Weber, F. P. (a) Case of Osteosclerotic Anemia or Leukemia, *M. Press* **127** 74, 1929, (b) Specimens from a Case of Osteosclerotic Anemia or Leukemia, *Tr. M. Soc. London* **52** 99, 1929.

15 Zahn, F. W. Beiträge zur Geschwulstlehre, *Deutsche Ztschr. f. Chir.* **22** 1, 1885.

16 Gall, E. A. Benzene Poisoning with Bizarre Extra-Medullary Hematopoiesis, *Arch Path* **25** 315 (March) 1938.

17 (a) Hirsch, E. F. Generalized Osteosclerosis with Chronic Polycythemia Vera, *Arch Path* **19** 91 (Jan) 1935. (b) Hirschfeld, H. Die generalisierte aleukamische Myelose und ihre Stellung im System der leukamischen Erkrankungen, *Ztschr. f. klin. Med.* **80** 126, 1914. (c) Rosenthal, N., and Bassen, F. Course of Polycythemia, *Arch. Int. Med.* **62** 903 (Dec) 1938. (d) Stone, D. M., and Woodman, D. Polycythemia Terminating in Leukoerythroblastic Anemia, *J. Path. & Bact.* **47** 327, 1938. (e) Vaughan, J., and Harrison, C. V. Leukoerythroblastic Anemia and Myelosclerosis, *ibid.* **48** 339, 1939.

tosis, fluorine sclerosis<sup>5</sup> and related disorders. Osteopetrosis may be associated with other diseases, as in a case of Hodgkin's disease reported by Hersker and Stein<sup>6</sup>.

Osteopetrosis is frequently found during childhood, and the severe types are characterized by mental and physical retardation, weakness, atrophy of the optic nerve, hydrocephalus, poor dentition, progressive enlargement of the spleen, liver and lymph nodes, progressive development of a refractory type of anemia (associated usually with thrombopenia or leukopenia and often with slight myeloma), and occasionally by osteomyelitis and pathologic fractures. A symptomless type<sup>7</sup> has also been described. This condition remains unrecognized until roentgenograms are taken for other reasons. It has familial and hereditary features, and a history of consanguinity is frequent. The causation remains unknown. Karshner<sup>1</sup> stated the belief that the process is a primary hereditary dyscrasia of mesenchyme, and McCune and Bradley,<sup>35</sup> that it is an abnormality of the parental germ plasma. Osteopetrosis has been diagnosed in fetuses and in adults as late as the eighth decade. The prognosis varies, the patient may live a few weeks or many decades. The postmortem observations vary, but the usual pathologic changes observed have been those of hepatosplenomegaly, occasionally lymphadenopathy and very dense bone (markedly resistant to sawing in most cases) have been seen, with a small or no medullary cavity. Microscopically the spleen, liver and lymph nodes are often diffusely fibrotic, and occasionally extramedullary hemopoiesis is present. The endosteum of most of the bones reveals a marked increase in the number and thickness of the trabeculae, which encroach on the marrow cavity, often to its exclusion. The periosteum may be involved too. The few spaces which may remain are usually filled with fibrous tissue or large cells resembling reticulum cells and only small deposits of hemopoietic tissue.

Myelofibrosis was first reported by Hueck<sup>8</sup> in 1879. Ante mortem his patient was known to have splenomegaly, leukocythemia and anemia, and post mortem, fibrosis of the spleen with foci of extramedullary hemopoiesis associated with myeloid hyperplasia and generalized fibrosis of the bone marrow. He felt that the patient had had two diseases, myeloid leukemia and osteosclerosis. Since 1879 there have been approximately 75 cases of this disease reported, the diagnosis having been made mainly post mortem. Most of these cases have been reviewed and discussed by Mozer,<sup>9</sup> Chapman,<sup>10</sup> Vaughan<sup>11</sup> and Carpenter and Flory.<sup>12</sup> Generalized fibrosis of the bone marrow and hyperplasia of the endosteum are the predominating pathologic features of this disease. The fibrosis may involve only the marrow cavity, or it may invade the endosteum, the cortex and even the

5 Wilkie, J. Fluorine Osteosclerosis, *Brit J Radiol* **13** 213, 1940.

6 Hersker, H., and Stein, J. J. Osteopetrosis Associated with Hodgkin's Disease, *Am J Roentgenol* **43** 74, 1940.

7 (a) Kretzmar, J. H., and Roberts, R. A. Case of Albers-Schonberg's Disease, *Brit M J* **1** 837, 1936. McPeak<sup>34</sup> (b) Wortis, H. Osteopetrosis (Marble Bones), *Am J Dis Child* **52** 1148 (Nov.) 1936.

8 Hueck, G. Zwei Falle von Leukämie mit eigenthümlichen Blut resp. Knochenmarks-befund, *Virchows Arch f. path. Anat.* **78** 475, 1879.

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The blood count was red cells 2,430,000, white cells 16,250, and platelets 80,000. The differential count was nonsegmented neutrophils 15 per cent, segmented neutrophils 24 per cent, neutrophilic myelocytes 6 per cent, myeloblasts 6 per cent, basophils 1 per cent, lymphocytes 44 per cent, monocytes 4 per cent, erythroblasts 11 per hundred white cells, normoblasts 8 per hundred white cells and reticulocytes 10 per cent. There was 44 per cent hemoglobin. The results of the urinalysis and the Takata-Ara and Wassermann tests were negative. Chemical examination of the blood revealed phosphorus 6 mg, calcium 112 mg and sugar 80 mg per hundred cubic centimeters, phosphatase 126 King-Armstrong units, serum albumin 44 per cent, and globulin 27 per cent. On roentgenographic examination all of the bones showed the typical diffuse and severe density. Roentgenograms of the long bones (fig 1) had no shadows representing medullary cavities, but transverse striations and old fracture sites were present.

*Sternal Puncture*—A sternal puncture was attempted, but because of the inability to penetrate the outer plate of the sternum with the aspiration needle a tentative diagnosis of osteopetrosis was made. The diagnosis was confirmed later by roentgenograms of the osseous system.

*Course*—The child transitorily improved after transfusions, but in general the clinical course was unsatisfactory.

## 2 MYELOFIBROSIS (MYELOSCLEROSIS, LEUKOERYTHROBLASTIC ANEMIA, OSTEOSCLEROTIC ANEMIA)

### A MYELOFIBROSIS WITH REFRACTORY ANEMIA WITHOUT ROENTGENOGRAPHIC CHANGES OF OSSEOUS SYSTEM

*CASE 2—History*—I C, a white girl aged 4 months, was admitted to the hospital service of Dr Schick, on Jan 3, 1926. A history of a normal delivery was obtained. The child appeared normal at birth and was breast fed for two months. A supplement of cow's milk was given during the following two months. The patient gained weight until two weeks previous to admission. At that time she began to lose her appetite and became weak, inactive, pale and constipated. An irregular elevation of temperature was noted. There were no hemorrhagic tendencies.

*Physical Examination*—The patient was moderately well nourished, with marked pallor. The spleen and the liver were barely palpable. Many small shotty cervical lymph nodes could be palpated. The reactions to Wassermann and tuberculin tests were negative and the results of urinalyses normal. Roentgenograms of the thorax and of the long bones were normal. The value for hemoglobin was 20 per cent, for red blood cells 1,120,000, for white blood cells 10,000 and for platelets 150,000. The differential count was polymorphonuclear neutrophils 40 per cent, neutrophilic myelocytes 3 per cent, myeloblasts 1 per cent, lymphocytes 53 per cent, monocytes 3 per cent, megaloblasts 1 per hundred white cells, normoblasts 2 per hundred white cells and reticulocytes 4 per cent.

*Biopsy*—The marrow of the right tibia was markedly fibrotic and was infiltrated with lymphoid cells.

*Course*—Four transfusions failed to increase the hemoglobin level, and the child died thirty days after admission. Permission for autopsy could not be obtained.

*CASE 3<sup>18</sup>—History*—E G, a white girl 4 months of age, was admitted to the Beth Israel Hospital,<sup>18</sup> Newark, N J, on Nov 11, 1933 with a history of pallor, anorexia and vomiting of one month's duration. The patient was a full term child, normally delivered, having a birth weight of 7 pounds and 13 ounces (3,534 Gm). She took nourishment well and gained weight for the first three months. The onset of symptoms was gradual, without the accompaniment of fever or hemorrhage.

*Examination*—The patient was well developed but pale and lay listlessly in bed. The spleen and the liver were barely palpable. Roentgen examination of the chest revealed an ovoid heart, suggestive of a cardiac anomaly. The skeletal system had no abnormalities roentgenologically.

The blood count showed red cells 1,050,000, white cells 7,100 and platelets 240,000, with a differential count of polymorphonuclear neutrophils 5 per cent, metamyelocytes 1 per cent, lymphocytes 86 per cent and monocytes 8 per cent. There was 16 per cent hemoglobin. The result of a fragility test of red blood cells was normal. The bleeding time and the coagulation time were within normal limits.

<sup>18</sup> Dr Rosenberg of the pediatric service of Beth Israel Hospital gave permission to publish this case.

A With refractory anemia without roentgenographic changes of the osseous system

B With associated myeloma

- (a) Leukopenia or normal white blood cell levels without roentgenographic changes of the osseous system
- (b) Leukopenia or normal white blood cell levels with roentgenographic changes
- (c) Leukocytthemia without roentgenographic changes
- (d) Leukocytthemia with roentgenographic changes

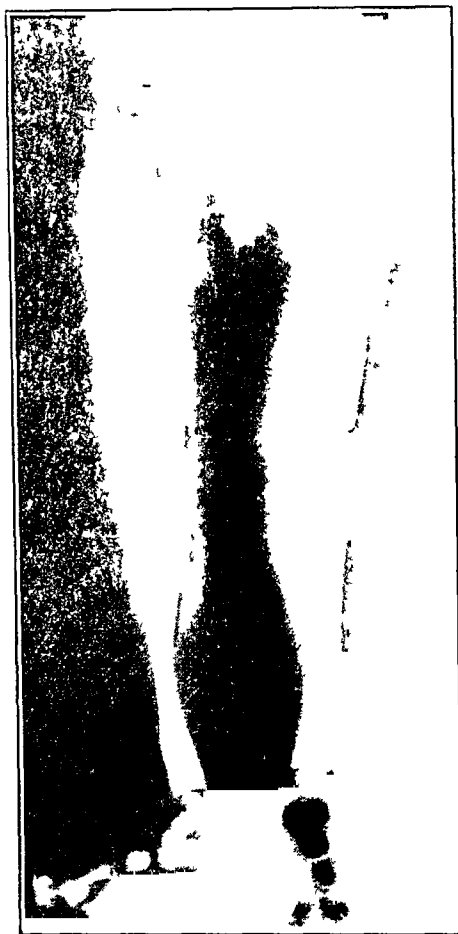


Fig 1 (case 1) —Osteopetrosis, diffuse density of the bones

C With associated "spent" polycythemia

- (a) Without roentgenographic changes of the osseous system
- (b) With roentgenographic changes of the osseous system

A summary of the observations in the cases of myelofibrosis are presented in the accompanying table

#### 1 OSTEOPETROSIS (ALBERS SCHONBERG, OR MARBLE BONE DISEASE)

CASE 1—*History and Examination*—B K, an 18 month old boy, was observed in the consultation service on Dec 2, 1937. There was a history of retarded physical and mental development, a progressive enlargement of the spleen and liver and an associated progressive pallor. The patient was a thin, pale, inactive child with a prominent abdomen. The edge of the liver was felt 6 cm below the right costal margin and the edge of the spleen 3 cm below the left costal margin.

*Biopsy*—The tibial bone marrow was markedly hypoplastic, with only a few scattered foci of erythroblasts and myeloblasts present. Fibrosis was extensive and was associated with an excess of bony trabeculae (fig 2).

*Course*—With frequent transfusions and with iron and liver therapy the hemoglobin level rose to 80 per cent. The total white cell count and differential count did not change, 90 per cent of the white cells were lymphocytes. Within three weeks the temperature became elevated in association with bloody stools and jaundice. There was some evidence of pulmonary edema, and the child died on December 26. The final blood count was red blood cells 3,500,000 and white blood cells 1,900, with lymphocytes 86 per cent and monocytes 14 per cent, the hemoglobin amounted to 49 per cent. Permission for an autopsy could not be obtained.

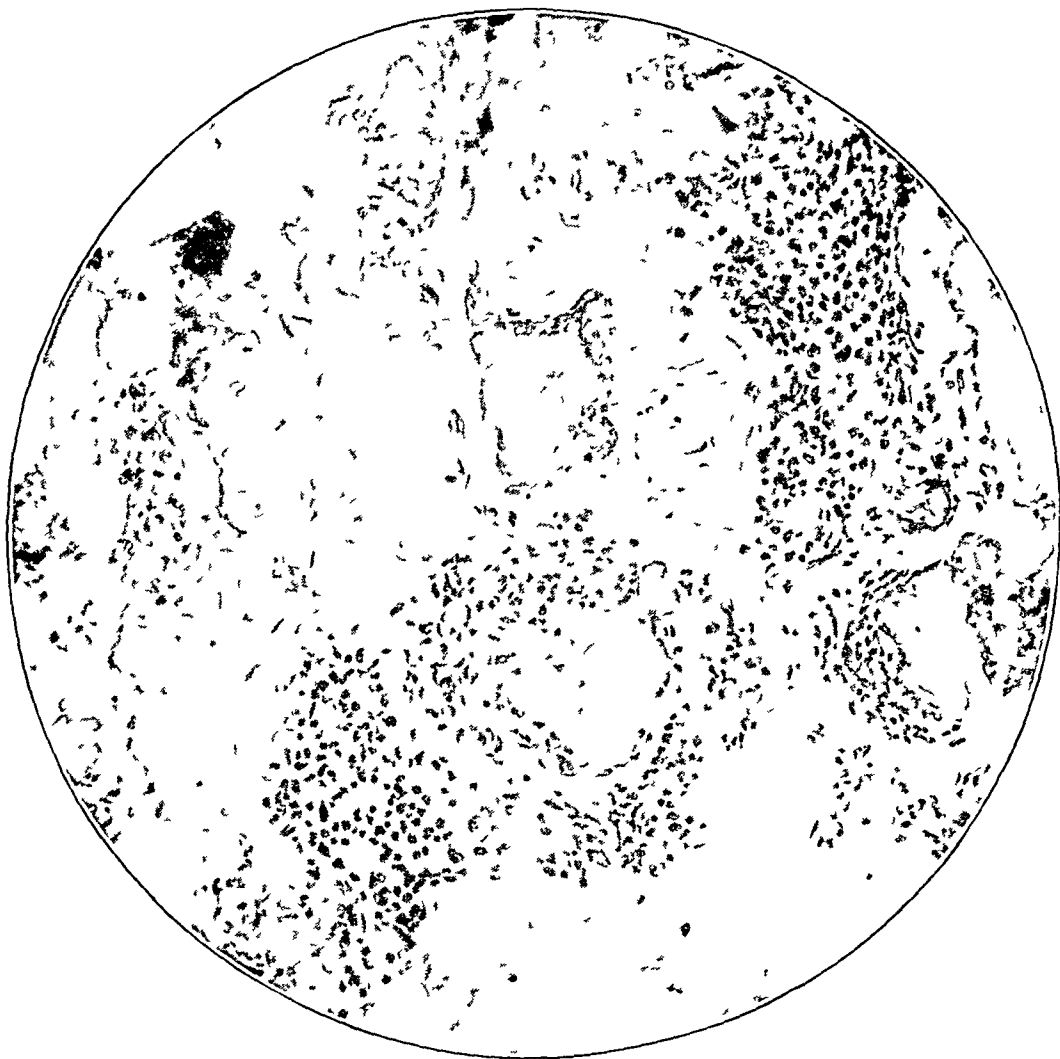


Fig 2 (case 3) —Tibial bone marrow, showing myelofibrosis

*CASE 4—History*—S K, a white girl aged 10 years, was admitted to the hospital on Nov 24, 1929. The past history was irrelevant. The present illness started four weeks before admission, with anorexia, pallor and loss of weight. Two weeks later fever and tarlike stools appeared. On admission the patient had these complaints with the addition of sore throat and puffiness of the tissues about the knees and ankles.

*Physical Examination*—The patient was a well developed girl with pronounced pallor, fundal hemorrhages, edema of the ankles and palpable enlargement of the spleen, liver and peripheral lymph nodes. The results of clinical examination of the blood and examination of the stool and urine were normal, cultures of material from the throat were negative. The roentgenograms of the long bones revealed no abnormalities. The hemoglobin content was 12 per cent, the red blood cells numbered 1,090,000 and the white blood cells 1,900, with platelets 12,000, segmented polymorphonuclear leukocytes 3 per cent, lymphocytes 96 per cent and monocytes 1 per cent. A clinical diagnosis of subleukemic lymphatic leukemia was suggested.

*Summary of Findings in Cases of Myelofibrosis*

Case	Sex	Age	Palpable Enlarge- ment of Spleen	Palpable Enlarge- ment of Liver	Palpable Enlarge- ment of Lymph Nodes	Hemo- globin, %	Red Blood Cells, per Cu Mm	White Blood Cells, per Cu Mm	Myelocytes and Myelo- blasts in Peripheral Blood	Normo blasts in Peripheral Blood	Results of Marrow Biopsy	Roentgen Changes in Osseous System	Changes in Marrow Seen at Autopsy
2	F	1 mo	Slight	Slight	Shotty	20	1,120	10,000	Occ	Occ	Tibia fibrosis with infiltration of lymphoid cells	Normal	No autopsy
3	F	4 mo	No	No	No	16	1,050	7,100	Occ	No	Tibia extensive fibrosis	Normal	No autopsy
4	F	10 yr	Yes	Yes	Yes	12	1,090	1,900	No	No	Tibia moderate fibrosis	Normal	No autopsy
B With Associated Myelemia													
5	F	16 mo	Yes	Yes	Yes	22	1,500	1,700	Yes	Occ	No	Normal	Generalized fibrosis of marrow
6	F	53 yr	Yes	Yes	Yes	72	4,170	9,800*	Yes	Occ	No	Normal	Generalized fibrosis of marrow
7	M	59 yr	Yes	Yes	Yes	75	4,224	7,600	Yes	Yes	Sternum diffuse fibrosis	Normal	No autopsy
8	M	55 yr	Yes	No	No	30	2,050	2,900	Yes	Yes	Sternum marked fibrosis	Normal	No autopsy
9	M	52 yr	Yes	No	No	78	4,100	7,200	Yes	Yes	Sternum moderate fibrosis	Normal	Patient still under observation
(a) Leukopenia or Normal White Blood Cell Levels Without Roentgenographic Changes of the Osseous System													
10	F	67 yr	Yes	Yes	No	28	2,260	4,400	Yes	Yes	Sternum diffuse fibrosis	Osteoporosis of many bones	No autopsy
11	M	53 yr	Yes	No	No	52	3,560	4,000	Yes	Yes	Sternum marked fibrosis	Periosteum of femur split laterally	No autopsy
12	M	25 yr	Yes	No	No	56	3,750	8,800	Yes	Yes	Sternum, marked fibrosis	Refractation of all bones	No autopsy
13	F	53 yr	Yes	Yes	No	58	3,670	5,000	Yes	Yes	Sternum focal fibrosis	Osteoporosis and sclerosis	Patient still under observation
14	M	40 yr	Yes	No	Yes	34	3,150	227,000	Yes	Occ	No	Normal	Generalized fibrosis of marrow
15	M	53 yr	Yes	Yes	Yes	53	3,100	23,000	Yes	Yes	No	Mottling of all bones	Humeral marrow diffuse fibrosis
16	M	47 yr	Yes	Yes	Yes	50	2,970	38,000	Yes	Yes	Sternum diffuse fibrosis	Mottling of all bones	
C With Associated "Spent" Polycythemia													
17	F	47 yr	Yes	Yes	No	69	3,500	10,100	Yes	Yes	Sternum diffuse fibrosis	Normal	Sarcomatous changes of the marrow
18	M	56 yr	Yes	Yes	Yes	56	3,100	8,100	Yes	Yes	Sternum, diffuse fibrosis	Mottling of all bones	No autopsy

\* Terminally the white blood count rose to 120,000

*Autopsy*—The essential microscopic observations were coronary sclerosis, fatty and myeloid infiltration of the liver, myeloblastic infiltration of the splenic sinuses and vascular degeneration of the kidneys. Most of the bone marrow was replaced by bony trabeculae and fibrous tissue, and there were few foci of myelocytes or myeloblasts.

*CASE 7—History*—P. G., a white man 59 years old, was admitted to the hospital on June 28, 1926. In 1919 he had been informed by his family physician that he had an enlarged spleen. Six months before admission he noted increasing generalized weakness, an increasing deep-seated pain in the lower part of the back and a tumor in the left upper quadrant of the abdomen. His friends noted that his complexion had become yellowish.

*Physical Examination*—The patient was well nourished, icteric and afebrile. The liver was firm and extended 4 fingerbreadths below the costal margin and the spleen 6 cm below the left costal margin. The peripheral nodes were enlarged. The urine was normal except for large quantities of urobilin. The result of a bromsulphalein test was normal. Examination of the blood showed urea 26 mg and uric acid 62 mg per hundred cubic centimeters, hemoglobin 75 per cent, red cells 4,224,000, white cells 7,600 and platelets 210,000, with neutrophils 55 per cent, neutrophilic myelocytes 3 per cent, myeloblasts 3 per cent, eosinophils 4 per cent, basophils 5 per cent, lymphocytes 27 per cent, monocytes 3 per cent and megaloblasts 2 per hundred white cells. A diagnosis was made of leukopenic myeloid leukemia with hepatic and renal infiltrations.

*Biopsy*—The sternal marrow was diffusely fibrotic. A few islands of myeloid cells were present.

*Course*—The patient attended the hematologic outpatient department regularly for two years after his discharge. He showed little change except that on April 25, 1928 the basal metabolic rate was  $-17$  per cent. He was given thyroid, and on his second admission, one year later, on April 8, 1929, the basal metabolic rate was  $+20$  per cent. At this time he complained of progressive weakness and dyspnea. The spleen filled two thirds of the abdomen. The hemoglobin content was 47 per cent, the red blood cells numbered 2,380,000, the white blood cells 5,800 and the platelets 180,000, with neutrophils 54 per cent, neutrophilic myelocytes 3 per cent, neutrophilic eosinophils 2 per cent, neutrophilic basophils 1 per cent, myeloblasts 2 per cent, eosinophils 4 per cent, basophils 5 per cent, lymphocytes 25 per cent and monocytes 4 per cent. Roentgen examinations of the ribs and bones of the upper extremities gave normal results. The patient was discharged from the hospital unimproved. He had a gradual down-hill course and died in 1936, seventeen years after the onset of his disorder. Permission for an autopsy was not obtained.

*CASE 8—History*—H. C., a white man aged 55, complained of marked precordial pain and dyspnea. He was first seen on Feb 27, 1939. He had been known to have syphilis and had received many courses of antisyphilitic treatment. After the last course he complained of the aforementioned symptoms.

*Physical Examination*—The patient was well developed, well nourished, pale and dyspneic. The spleen extended 2 fingerbreadths below the left costal margin. The liver was not palpable. There was no lymphadenopathy. Petechiae were present in the skin and mucous membranes. The hemoglobin content of the blood was 30 per cent. The red blood cells numbered 2,050,000, the white blood cells 2,900 and the platelets 40,000, with polymorphonuclear leukocytes 65 per cent, myelocytes 4 per cent, myeloblasts 3 per cent, eosinophils 1 per cent, lymphocytes 23 per cent, monocytes 4 per cent, normoblasts 3 per hundred white blood cells and reticulocytes 2 per cent. The icterus index was 2. The Kahn reaction was 4 plus. Coagulation time was ten minutes. Roentgen examination of the osseous system showed nothing abnormal.

*Biopsy*—The sternal marrow was markedly fibrotic.

*Course*—The patient was at first thought to have aplastic anemia following neoarsphenamine therapy. The examination of the biopsy specimen showed that such a diagnosis was not correct. Transfusions were given and were followed by temporary improvement. The patient died eleven months after the onset of the symptoms. An autopsy was not permitted.

*CASE 9—History*—J. H., a white man aged 52, was admitted to the hospital on April 28, 1933 with a history of weakness and a chronic hacking cough. From then until 1941 the weakness became progressively worse and pallor was more noticeable.

*Physical Examination*—The patient was well developed and pale. A firm, nontender spleen extended 3 fingerbreadths below the left costal margin. Neither the liver nor the peripheral lymph nodes were palpably enlarged. There were no petechiae present. The hemoglobin content of the blood was 78 per cent. Examination of the blood showed red cells 4,120,000, white cells 7,200 and platelets 450,000, with polymorphonuclear leukocytes 65 per cent, myeloblasts 6 per cent, myelocytes 7 per cent, eosinophils 2 per cent, basophils 3 per cent, lymphocytes



*Biopsy*—The tibial bone marrow was moderately fibrotic. Some foci of undifferentiated mononuclear cells were present.

*Course*—Two transfusions (250 cc each) were given, and the mucous membrane of the pharynx, which had started to undergo ulceration, improved markedly. Four more transfusions were given but the blood levels did not rise, and the patient died December 30. An autopsy was not permitted.

#### B MYELOFIBROSIS WITH ASSOCIATED MYELOMA

##### (a) *Leukopenia or Normal White Blood Cell Levels Without Roentgenographic Changes of the Osseous System*

*CASE 5—History*—D. S., a white girl 16 months old, entered the hospital on July 11, 1922. The child was normal at birth and remained well until she reached the age of 7 weeks. At that time chronic bronchopneumonia developed. Recovery was slow. She had acute gastroenteritis when 3 months old. She vomited daily, and the vomiting was associated with anorexia and loss of weight. Four days before admission the temperature became elevated, with enlargement of the peripheral nodes.

*Physical Examination*—The patient was emaciated and had puffy eyelids. There were petechiae on the hard palate. Both the spleen and the liver extended  $3\frac{1}{2}$  fingerbreadths below the costal margin. All of the peripheral lymph nodes were enlarged. The results of many chemical analyses of the blood and examinations of the stool and urine were normal. The hemoglobin content was 22 per cent, the red blood cells numbered 1,500,000 and the white blood cells 1,700, with neutrophils 13 per cent, neutrophilic myelocytes 6 per cent, lymphocytes 77 per cent and monocytes 4 per cent. The reaction to a tourniquet test was positive, and the bleeding time was six minutes. The results of roentgen examinations of the chest and upper extremities were normal.

*Course*—Transfusions were given without avail. Death occurred on August 1.

*Autopsy*—The markedly enlarged liver, spleen and lymph nodes all had a homogeneous appearance on cut section. Microscopically these organs were diffusely infiltrated with myeloid cells and nucleated red cells. The bone marrow was largely replaced by fibrous tissue.

*CASE 6—History*—M. D., a white woman 53 years old, was admitted to the hospital on May 5, 1920. She had had an oophorectomy in 1914 but otherwise had been in good health until six weeks previous to admission, when a constant severe localized pain developed in the upper left quadrant of the abdomen. It was not affected by eating and was not accompanied by nausea or vomiting. She complained, however, of weakness and anorexia.

*Physical Examination*—The patient was a well developed, undernourished woman with moderate pallor. The spleen was tender and extended 2 cm below the left costal margin, the liver extended 3 cm below the right costal margin. A few small inguinal glands were palpable. The Wassermann reaction was negative. There was no free hydrochloric acid in the stomach contents, the total acidity amounted to 16. The blood urea was 17 mg and the cholesterol 522 mg per hundred cubic centimeters. The basal metabolic rate was normal. The results of roentgen examination of the gastrointestinal system, osseous system and genitourinary tracts were normal. The hemoglobin content of the blood was 72 per cent, the red blood cells numbered 4,170,000, the white blood cells 9,800 and the platelets 250,000, with a differential count of neutrophils 68 per cent, neutrophilic myelocytes 13 per cent, myeloblasts 5 per cent, eosinophils 1 per cent, lymphocytes 10 per cent and monocytes 2 per cent. A diagnosis of leukopenic myeloid leukemia was made.

*Course*—The patient was discharged and referred to the hematology clinic, which she attended regularly for eight years. Roentgen therapy and solution of potassium arsenite U. S. P. were occasionally given during that period. The blood count did not change until January 1927 (seven years after the first admission), when there was an increase in the total white cell count to 17,600. A year and a half later, June 1928, the white cell count rose to 22,000. The spleen and liver gradually increased in size. Dyspnea occurred on exertion. Because of these gradual changes and the loss of general strength, the patient was readmitted on August 28. Bronchopneumonia in the lower lobes of both lungs was discovered. The results of roentgen examination of the ribs and bones of the upper and lower extremities were normal. The spleen extended to the iliac crest, and the liver extended to the level of the umbilicus. The blood count was: red cells 2,850,000, white cells 124,000 and platelets 100,000, with neutrophils 80 per cent, neutrophilic myelocytes 10 per cent, myeloblasts 3 per cent, eosinophils 3 per cent, lymphocytes 2 per cent, monocytes 2 per cent and normoblasts 24 per hundred white cells. There was 57 per cent hemoglobin. After a transfusion the patient improved. Three weeks later cardiac decompensation developed suddenly, and the patient died on September 18.

**CASE 10—History**—S G, a white woman 67 years old, was admitted to the hospital in Dec 2, 1934. She had known for sixteen years that she had an enlarged spleen. For one year previous to admission she complained of gradual progressive weakness, loss of weight and increasing pallor. Ecchymoses, nosebleeds and lumbar pains increased in number and intensity six months before admission.

**Physical Examination**—The patient was thin and emaciated, with a yellowish pallor. The spleen extended to the iliac crest. It was smooth, firm, nontender and movable. The liver was firm and extended 8 cm below the right costal margin. The Wassermann reaction was negative and the icteric index 12. Examination of the blood showed total proteins 6.4 Gm, sugar 150 mg, cholesterol 150 mg and cholesterol esters 36 mg per hundred cubic centimeters, hemoglobin 38 per cent, red blood cells 2,260,000, white blood cells 4,400, platelets 60,000, and a differential count of nonsegmented polymorphonuclear leukocytes 9 per cent,

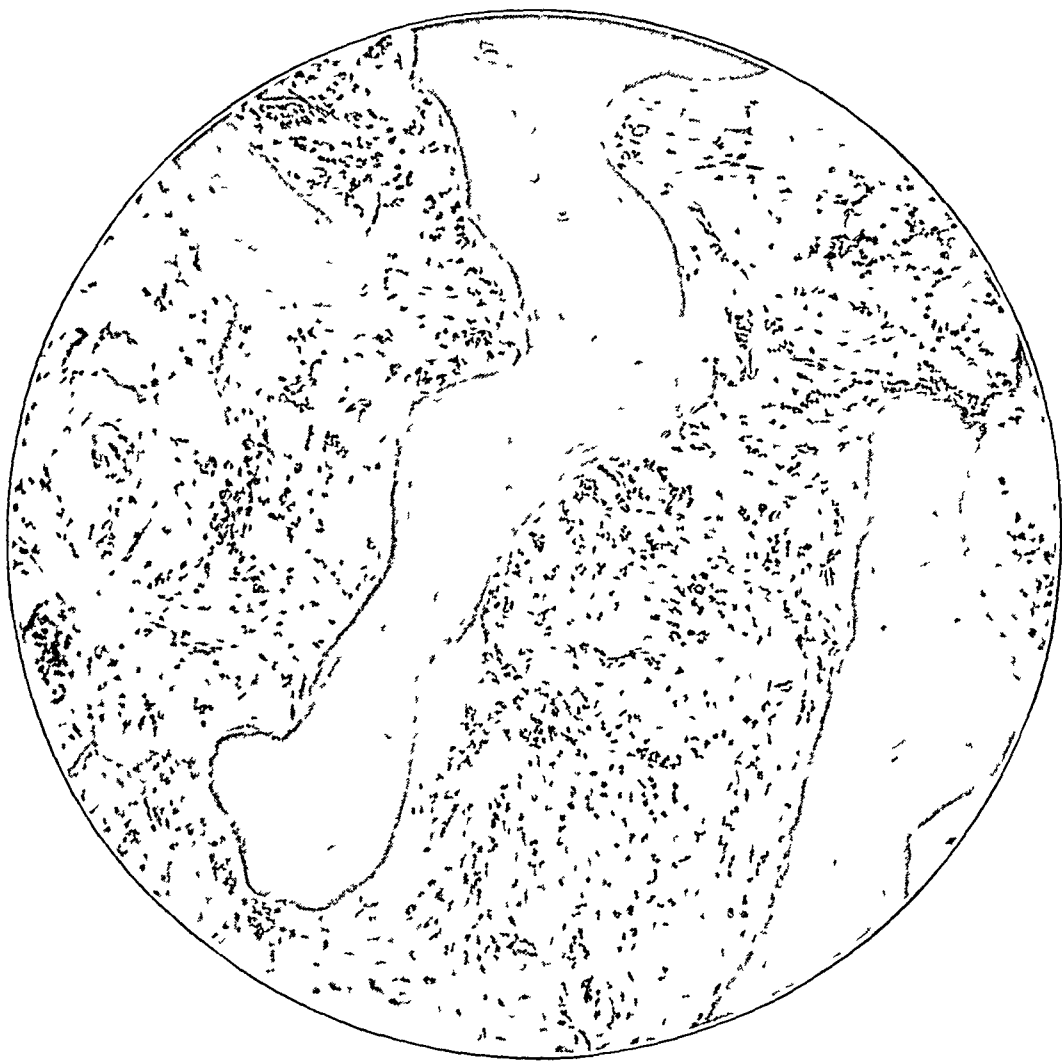


Fig 4 (case 11) —Diffuse fibrosis of sternal marrow

segmented polymorphonuclear leukocytes 38 per cent, neutrophilic myelocytes 16 per cent, myeloblasts 4 per cent, lymphocytes 30 per cent, monocytes 3 per cent, normoblasts 17 per hundred white cells and erythroblasts 4 per hundred white cells. As revealed by roentgenologic examination, the femurs were widened above the condyles and had irregular, mottled transparencies in the medulla at this point. The latter characteristic was also observed in the upper third of the femurs and the upper halves of the tibiae. There was a generalized osteoporosis of the lumbar vertebrae and pelvic bones.

**Biopsy**—Small islands of erythroblasts and myeloblasts scattered throughout an extensive fibrosis were found in place of normal sternal bone marrow.

**Course**—The patient was sent to a convalescent hospital after the diagnosis of myelofibrosis was made. Transfusions were given when necessary. She died one year after discharge.

**CASE 11—History**—W E, a white man aged 53, was admitted to the hospital on Jan 8, 1935. He had been in good health until five years previous to admission, when he noted

12 per cent, monocytes 3 per cent and normoblasts 2 per hundred white blood cells. The Wassermann reaction was negative. Roentgen examination of the osseous system showed nothing abnormal. A sternal puncture in June 1939 showed white cells 24,000, megakaryocytes 22, myeloblasts 16 per cent, neutrophilic myelocytes 28.6 per cent, myelocytic eosinophils 0.3 per cent, nonsegmented polymorphonuclear leukocytes 14.3 per cent, segmented polymorphonuclear leukocytes 38 per cent, polymorphonuclear eosinophils 0.3 per cent, polymorphonuclear basophils 0.3 per cent, hematogones 3.6 per cent, lymphocytes 0.3 per cent, erythroblasts 1.6 per cent and normoblasts 11 per cent. Because the observations on the marrow were unsatisfactory for establishing a diagnosis, a biopsy of the sternum was carried out.

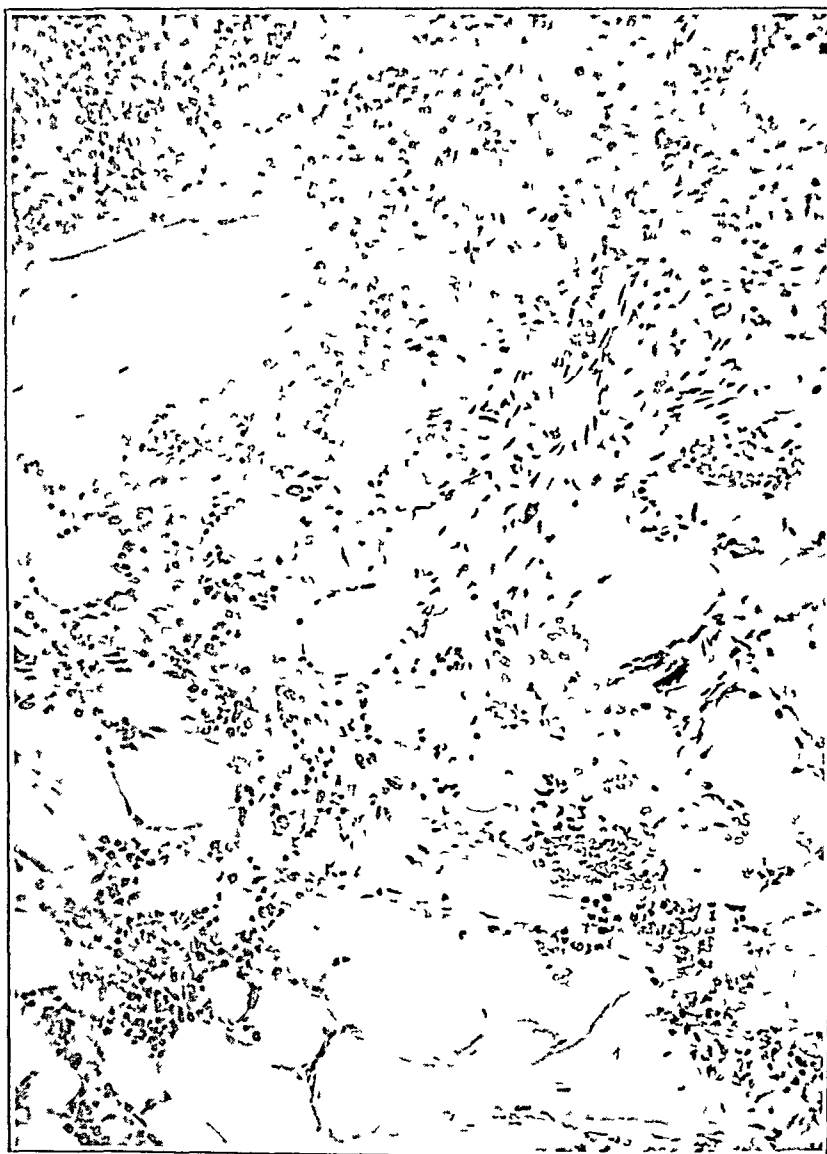


Fig 3 (case 9) —Early stage of fibrosis of sternal marrow

*Biopsy*—In July 1939 the sternal bone marrow was moderately fibrotic. Increased numbers of megakaryocytes were present and some foci of active hemopoiesis, especially of the erythrocytic series (fig 3).

*Course*—A blood count in June 1940 was as follows: hemoglobin 73 per cent, red cells 4,590,000, white cells 10,000 and platelets 200,000, with myelocytic neutrophils 15 per cent, nonsegmented polymorphonuclear leukocytes 10 per cent, segmented polymorphonuclear leukocytes 72 per cent, polymorphonuclear eosinophils 0, polymorphonuclear basophils 0, lymphocytes 11.5 per cent and monocytes 5 per cent. The patient is still under observation at the time of writing.

(b) *Leukopenia or Normal White Blood Cell Levels with Roentgenographic Changes of the Osseous System*

bones. The blood phosphatase amounted to 11 King-Armstrong units and the blood calcium and phosphorus to 9.4 mg and 4.4 mg, respectively, per hundred cubic centimeters.

*Biopsy*—A biopsy of the sternum April 1940 revealed focal fibrosis of the marrow and thickening of the bony trabeculae.

*Splenic Punctures*—Splenic punctures revealed myeloid metaplasia. Smears appeared not unlike those obtained on sternal puncture, showing immature and mature cells of the myeloid series, normoblasts, erythroblasts and a moderate number of megakaryocytes.

(c) *Leukocythemia without Roentgenographic Changes*

*CASE 14—History*—L. B., a white man aged 40, was admitted to the hospital on July 12, 1919. He had been in good health until April 1915, when enlargement of the spleen developed. Roentgen therapy at that time reduced the size of the spleen, and the patient felt better and remained improved until three months before admission. He complained of dimness of vision, dyspnea, night sweats, "burning" in the epigastrium, pain in the left scapular region and gradually increasing pain in the left upper quadrant of the abdomen.

*Physical Examination*—The patient was moderately well nourished and pale, with corneal opacities. The spleen extended 2 fingerbreadths below the level of the umbilicus. The liver was not palpable, but the peripheral lymph nodes were. The Wassermann reaction was negative. The blood urea content was 12 mg per hundred cubic centimeters. The hemoglobin content was 34 per cent. The red blood cells numbered 3,450,000, the white blood cells 227,000 and the platelets 114,000, with a differential count of neutrophils 37 per cent, neutrophilic myelocytes 42 per cent, eosinophils 4 per cent, basophils 10 per cent, lymphocytes 4 per cent and monocytes 3 per cent. On roentgen examination the long bones appeared normal.

*Course*—Because of the previous response to roentgen therapy, it was again tried with some success. In ten days the hemoglobin amounted to 71 per cent and the red blood cells numbered 3,480,000 and the white blood cells 7,200, with neutrophils 82 per cent, neutrophilic myelocytes 5 per cent, lymphocytes 9 per cent and monocytes 4 per cent. The patient felt better and left the hospital. He returned three months later, Dec. 1, 1919, with the complaints of headache, progressive weakness, vomiting, insomnia, dyspnea, palpitation and tinnitus. The liver was enlarged, extending 1 fingerbreadth below the right costal margin. The spleen and the lymph nodes were enlarged to the size observed on the previous admission. The hemoglobin content was 14 per cent. The red blood cells numbered 1,040,000, the white blood cells 6,400 and the platelets 320,000, with neutrophils 66 per cent, neutrophilic myelocytes 13 per cent, basophilic myelocytes 5 per cent, myeloblasts 5 per cent, lymphocytes 9 per cent and monocytes 2 per cent. The patient did not improve after roentgen therapy and transfusions. He died in December 1919.

*Autopsy*—The essential microscopic observations were generalized fibrosis of the spleen with areas of myeloid hyperplasia and erythropoiesis, passive congestion of the liver with brownish pigmentation in the centers of the lobules and generalized fibrosis of the marrows of the femur, ribs and sternum.

(d) *Leukocythemia with Roentgenographic Changes*

*CASE 15—History*—A. S., a white man aged 53, was admitted to the hospital on Oct. 26, 1933. A rather sudden enlargement of the spleen was responsible for a mechanical intestinal obstruction. A splenic artery ligation was the operative procedure considered safest, since the patient had been treated for myeloid leukemia during the preceding four years.

*Physical Examination*—The patient was well developed but emaciated and pale, with a huge abdomen and marked edema of the legs. The spleen was hard but mobile, it filled over two thirds of the abdomen. The liver extended 4 fingerbreadths below the right costal margin. Generalized lymphadenopathy existed. Examination of the blood showed urea 33 mg and uric acid 3.5 mg per hundred cubic centimeters, hemoglobin 53 per cent, red cells 3,100,000, white cells 23,000, platelets 310,000 and a differential count of nonsegmented polymorphonuclear leukocytes 40 per cent, segmented polymorphonuclear leukocytes 33 per cent, neutrophilic myelocytes 13 per cent, myeloblasts 5 per cent, eosinophils 2 per cent, lymphocytes 7 per cent and normoblasts 3 per hundred white blood cells. Figure 5 illustrates the giant platelets found in the peripheral blood.

*Course*—After a Drosselung operation (a facial constriction of the splenic artery) the blood count changed little, except that the platelets rose to 1,200,000. The postoperative course was uneventful. The patient was discharged on November 30. Within two weeks the spleen decreased in size sufficiently to relieve the obstruction. However, within six months it began to enlarge again. The enlargement this time obstructed the return flow of blood from the lower extremities. The resulting edema of the legs, with gradual progressive generalized weakness plus dyspnea, brought the patient to the hospital to seek relief, on Nov. 22, 1934.

weakness, bone pain, especially in the lumbar region and thighs, generalized edema and "heaviness" of the lower extremities. These symptoms gradually increased in severity. Four weeks before the patient's admission pains developed in the right and left upper quadrants of the abdomen, associated with a severe chronic backache.

*Physical Examination*—The patient was well developed and pale with slight edema of the face. The spleen extended 3 fingerbreadths below the costal margin. The liver was not palpable. The value for blood proteins was 7 Gm, for blood urea 11 mg, for blood calcium 10.9 mg and for blood phosphorus 3.8 mg, per hundred cubic centimeters, and that for blood phosphatase was 3.5 Bodansky units. The hemoglobin content was 52 per cent. The red blood cells numbered 3,860,000, the white blood cells 4,000 and the platelets 80,000, with non-segmented polymorphonuclear leukocytes 13 per cent, segmented polymorphonuclear leukocytes 41 per cent, neutrophilic myelocytes 5 per cent, myeloblasts 1 per cent, eosinophils 1 per cent, basophils 2 per cent, lymphocytes 35 per cent, monocytes 2 per cent, normoblasts 2 per hundred white blood cells and reticulocytes 5 per cent. The cortices of the femurs were split laterally and ventrally, while the remainder of the osseous system was normal roentgenographically.

*Biopsy*—During the sternal marrow puncture, a gritty sensation was perceived when the needle entered the marrow cavity, and no marrow could be withdrawn. The sternal biopsy revealed a diffuse fibrosis in the sternal marrow (fig 4).

*Course*—Transfusions were given monthly for over six years, and the patient died eleven years after the first symptoms appeared.

**CASE 12—History**—N. G., a white man aged 25, a physician, was admitted to the hospital on June 16, 1936 complaining of fatigue, weakness, pallor, edema of the ankles and pains in the long bones. The nonradiating pains were both dull and sharp. The fatigue and weakness had been complaints of the patient for a year, while the pains in the long bones were of four months' duration.

*Physical Examination*—The patient was well developed and apparently chronically ill. A soft blowing systolic hemic murmur was heard over the entire precordium. No enlargement of the liver or of the lymph nodes was discernible on palpation. A firm spleen extended 1 fingerbreadth below the costal margin. On admission the blood count was: red cells 3,750,000, white cells 8,800 and platelets 180,000. The differential count was: nonsegmented polymorphonuclear leukocytes 5 per cent, segmented polymorphonuclear leukocytes 56 per cent, neutrophilic myelocytes 8 per cent, myeloblasts 7 per cent, basophils 5 per cent, basophilic myelocytes 2 per cent, lymphocytes 11 per cent and monocytes 6 per cent, with normoblasts 1 and megaloblasts 1 per hundred white cells. The hemoglobin content was 56 per cent. Areas of rarefaction scattered throughout all the bones except those of the feet and hands were noted on the roentgenograms.

*Biopsy*—There was marked fibrosis of the sternal marrow.

*Course*—The patient had a chronic elevation of the temperature to between 99 and 100 F. Roentgen therapy was effective in reducing the size of the spleen very slightly. Transfusions and the administration of solution of potassium arsenite, U. S. P. and iron were ineffective in raising the hemoglobin level. The white cells varied little in number or quality. The patient's downward clinical course was similar to that of most leukemic patients. An autopsy was not permitted.

**CASE 13—History**—M. B., a 53 year old housewife, first noted an enlargement of the spleen in 1930. In 1936 she complained of weakness, nausea and vomiting.

*Physical Examination*—The patient was well developed, poorly nourished and pale. The inferior margin of the spleen was within 4 cm. of the iliac crest. In 1936 the blood count was: red cells 3,670,000, white cells 5,000 and platelets 160,000, with nonsegmented polymorphonuclear leukocytes 24 per cent, segmented polymorphonuclear leukocytes 33 per cent, neutrophilic myelocytes 5 per cent, myeloblasts 1 per cent, basophils 1 per cent, lymphocytes 33 per cent, monocytes 3 per cent and normoblasts 1 per hundred white blood cells. The hemoglobin content was 58 per cent.

*Sternal Puncture*—Several sternal punctures were made, and few cells were obtained. A tentative diagnosis of myelofibrosis was made.

*Course*—In 1937 the patient received injections for varicose veins, following which ulcers of the skin developed. The ulcers failed to heal until 1940. In 1940 the patient was much paler, the spleen extended into the pelvis and the liver extended 6 cm. below the costal margin. The blood findings were almost identical with those of 1936. Roentgenograms of the entire skeleton revealed disorganization of the trabecular structure, with irregular sclerosis of many

hormone. Numerous areas of mottling, condensation and rarefaction were noted in the roentgenograms taken of the skull, jaw, vertebrae, humerus (fig 6) and bones of the hands

*Biopsy*—The sternum had an increased number of bony trabeculae. The normal contents of the marrow were replaced by fibrous tissue in which there were many megakaryocytes (fig 7). Biopsy of a lymph node revealed chronic lymphadenitis with fibrosis.

*Splenic Puncture*—A smear of the aspirated material showed the presence of myeloid metaplasia with numerous myeloblasts, myelocytes and megakaryocytes.

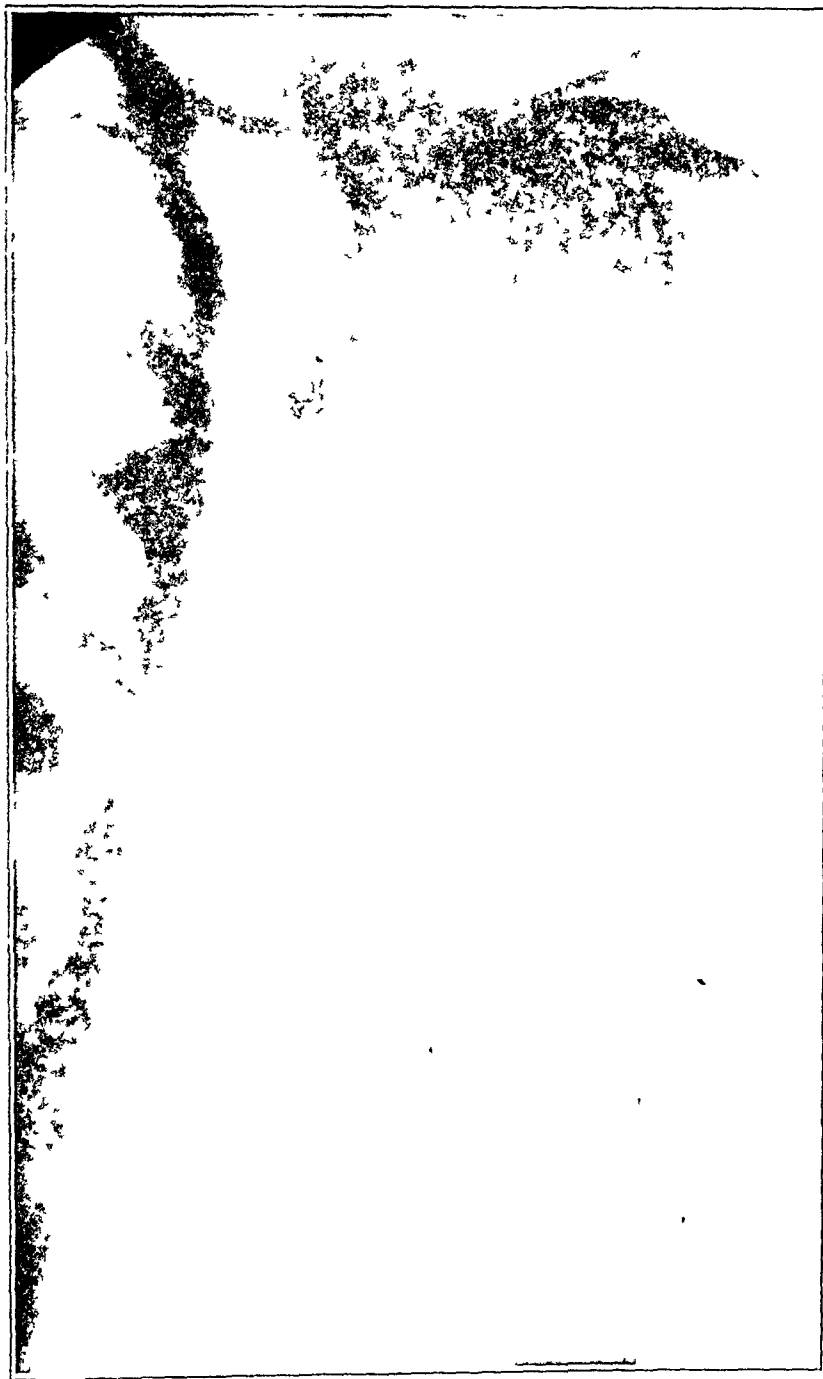


Fig 6 (case 16) —Numerous areas of mottling and rarefaction

*Treatment*—Pfeiffer and Gardner<sup>19</sup> were able to inhibit experimentally produced myelofibrosis of rats by the administration of testosterone propionate. For this reason testosterone

<sup>19</sup> Pfeiffer, C. A., and Gardner, W. U. Skeletal Changes and Blood Serum Calcium Levels in Pigeons Receiving Estrogens, *Endocrinology* **23** 485, 1938. Gardner, W. U., and Pfeiffer, C. A. Skeletal Changes in Mice Receiving Estrogens, *Proc Soc Exper Biol & Med* **37** 678, 1938, Inhibition of Estrogenic Effects on Skeleton by Testosterone Injections, *ibid* **38** 599, 1938.

The spleen again filled two thirds of the abdomen. Roentgen therapy was ineffective in reducing the size of the spleen. The blood count was similar to that on the first admission except that megakaryocytic fragments were frequently found in the peripheral blood, 1 per twenty white blood cells. On roentgen examination of the skeletal system a mottling of the vertebrae, ribs, scapulas, clavicles, humeri and iliac bones was noted. Marked ascites developed, and the patient died on December 25.

*Autopsy*—A partial autopsy was permitted. The bone marrow of the right humerus was diffusely fibrotic, and scattered throughout were islands of megakaryocytes. The spleen and liver showed the characteristic changes of megakaryocytic hepatosplenomegaly.

**CASE 16—History**—P. P., a white man aged 47, was admitted on Sept. 14, 1939 complaining of increasing swelling of the abdomen and generalized abdominal pain of five years

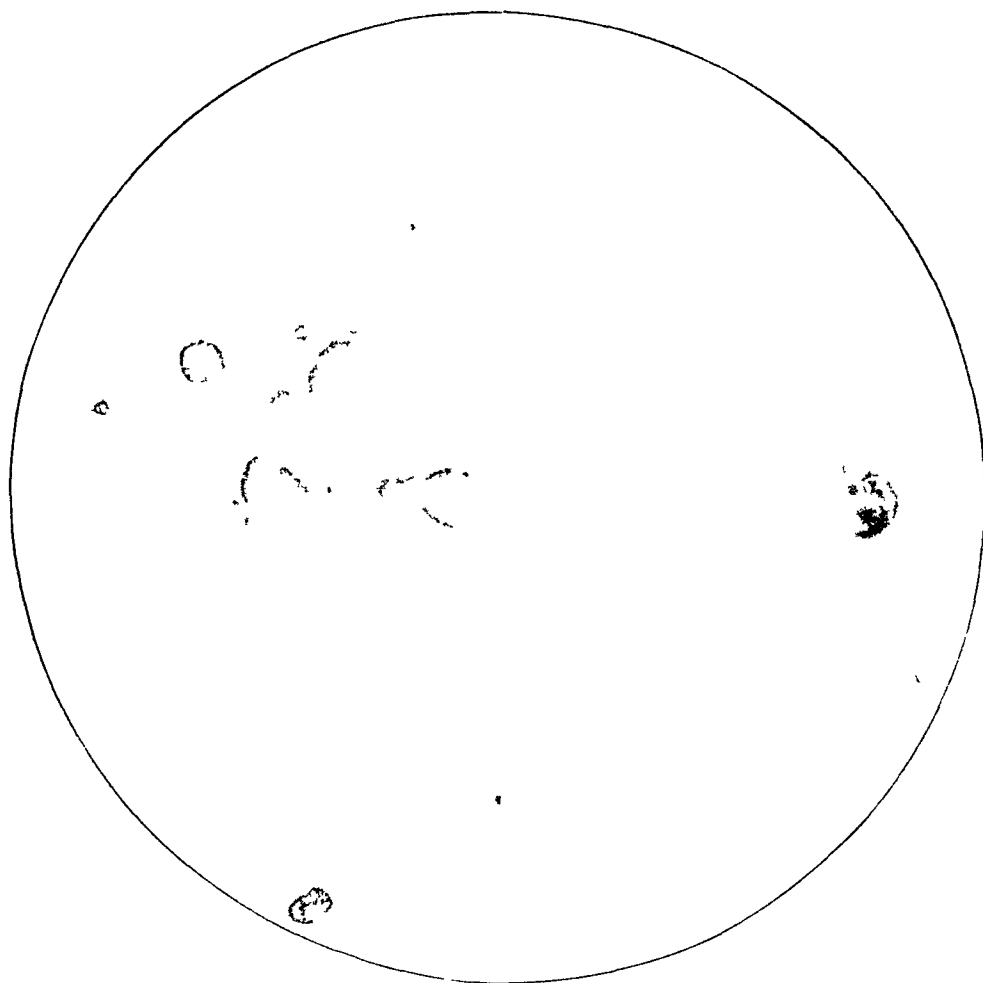


Fig. 5 (case 15)—Blood smear, showing megakaryocytic fragments and giant blood platelets.

duration. Sexual desire had been absent during this period. Two months before admission abdominal distress after meals became severe and dyspnea was marked.

*Physical Examination*—The patient was cachectic and had a sallow skin, little hair on any portion of the body and a prominent abdomen. The spleen extended to the iliac crest and the liver to the umbilicus. The hemoglobin content was 58 per cent. The red blood cells numbered 4,080,000, the white blood cells 9,250 and the platelets 150,000, and the differential count showed polymorphonuclear leukocytes 28 per cent, myelocytes 9 per cent, myeloblasts 9 per cent, eosinophils 4 per cent, lymphocytes 36 per cent and monocytes 14 per cent. There were 3 normoblasts per hundred white blood cells, 15 per cent reticulocytes and many elliptic and elongated red cells. Chemical examination of the blood showed uric acid 62 mg., cholesterol 140 mg. and calcium 83 mg. per hundred cubic centimeters. The Wassermann reaction was negative. The serum albumin amounted to 5.2 Gm. and the globulin to 1.6 Gm. per hundred cubic centimeters. The urine contained no increased excretion of male sex

*Physical Examination*—The patient was weak and pale, with a flabby musculature, but was fairly well developed and well nourished. The spleen extended 3 fingerbreadths below the costal margin. The liver was just palpable. The basal metabolic rate was  $-17$  per cent. The blood urea amounted to  $15$  mg, the blood cholesterol to  $310$  mg and the cholesterol esters to  $135$  mg per hundred cubic centimeters. The icterus index was  $11$ . Nearly all of the humors secretions and orifices were examined bacteriologically, without informative results. The hemoglobin was  $69$  per cent. The red blood cells numbered  $3,500,000$ , the white blood cells  $10,400$  and the platelets  $90,000$ . The differential count showed nonsegmented polymorphonuclear leukocytes  $10$  per cent, segmented polymorphonuclear leukocytes  $50$  per cent, neutrophilic myelocytes  $1$  per cent, myeloblasts  $5$  per cent, eosinophils  $2$  per cent, basophils  $1$  per cent, lymphocytes  $29$  per cent, monocytes  $2$  per cent and normoblasts  $2$  per hundred white cells. There were marked anisocytosis and poikilocytosis of the red cells, and many elliptic cells were found in the smears. Examinations of stools for parasites gave negative results. All roentgen examinations of the osseous system showed nothing abnormal.

*Sternal Puncture and Biopsy*—A gritty, crunchy sensation was noted when the aspiration needle entered the marrow cavity. No marrow fluid could be withdrawn. The sternal marrow removed for biopsy was diffusely fibrotic.

*Course*—The patient was discharged with the continuance of the unexplained chills and fever. It was decided that the anemia was a result of a "burnt-out" polycythemic process. The patient attended the hematologic outpatient clinic for injections of liver in an attempt to raise the hemoglobin level. After one of these injections a gluteal abscess developed. Later a chronic sloughing ulcer appeared at the site of the abscess, and a specimen for biopsy removed from the margin showed that the tissue was infiltrated with leukemic cells. The patient died six months after admission to the outpatient department.

*Autopsy*—Sarcomatous tissue replaced not only the fibrous tissue of the sternal marrow cavity but the marrow of all the bones. A diagnosis of myelosarcomatosis was made.

#### (b) With Roentgenographic Changes of the Osseous System

*CASE 18—History*—J. W., a white man aged  $56$ , was admitted to the hospital on Feb. 4, 1931. A diagnosis of polycythemia had been made thirteen years previously because the hemoglobin level was  $130$  per cent and the red blood cell count was  $9,500,000$ . The complaints at that time were headache, vertigo, abdominal enlargement and a thrombosis of the right middle toe which had become painfully gangrenous. Because of progressive enlargement of the spleen, lumbar pain and bloody urine, the patient was readmitted.

*Physical Examination*—The patient was small, thin and sharp featured, with a huge abdomen and small purpuric lesions over the lower extremities. General arteriosclerosis and ascites were present. The spleen extended into the iliac fossa, and the liver extended  $2\frac{1}{2}$  inches ( $6.3$  cm) below the costal margin. The peripheral lymph nodes were palpable. The basal metabolic rate was  $+34$  per cent. The icteric index was  $14$ . Examination of the blood showed urea  $22$  mg, cholesterol  $110$  mg, sugar  $115$  mg, calcium  $11$  mg and phosphorus  $37$  mg per hundred cubic centimeters, hemoglobin  $56$  per cent, red cells  $3,400,000$ , white cells  $8,100$  and platelets  $300,000$ , neutrophils  $59$  per cent, neutrophilic myelocytes  $5$  per cent, myeloblasts  $8$  per cent, basophils  $5$  per cent, lymphocytes  $15$  per cent, monocytes  $8$  per cent and normoblasts  $6$  per hundred white blood cells. Roentgenographically, the skull, the left femur, head of the right femur and the pelvic bones had a mottled appearance throughout. In a few areas there were erosions of the cortex of these bones.

*Biopsy*—The sternal marrow was diffusely fibrotic. A photomicrograph of this patient has been published.<sup>20</sup>

*Course*—The blood in the urine was due to an accumulation of uric acid crystals in the ureters, and the symptoms disappeared after ureteral washings. The patient was discharged feeling considerably better. After a two year downhill course, with gradually increasing anemia, he died suddenly. Permission for an autopsy could not be obtained.

#### COMMENT

Both osteopetrosis and myelofibrosis are uncommon disorders of unknown causation in which an abnormality within the osseous system, by one means or another, alters or displaces the contained hemopoietic tissue. In the former, the marrow cavity is often obliterated by an overgrowth of abnormal bone, while in the

<sup>20</sup> Rosenthal, N. Aplastic Anemia and Osteosclerosis, in Downey, H. Handbook of Hematology, New York, Paul B. Hoeber, Inc., 1937, vol. 3, sect. 29, pp. 2201-2230.



propionate was administered to this patient, who apparently responded favorably for 100 months. Then there was a rapid decline, clinically, and the patient died on June 6, 1940, before a satisfactory amount of the androgen had been administered.

#### C MYELOFIBROSIS WITH ASSOCIATED "SPENT" POLYCYTHEMIA

##### (a) *Without Roentgenographic Changes of the Osseous System*

CASE 17—*History*—M. W., a white woman aged 47, was admitted to the hospital on July 10, 1935. This patient had a most interesting past history. When a small girl she was

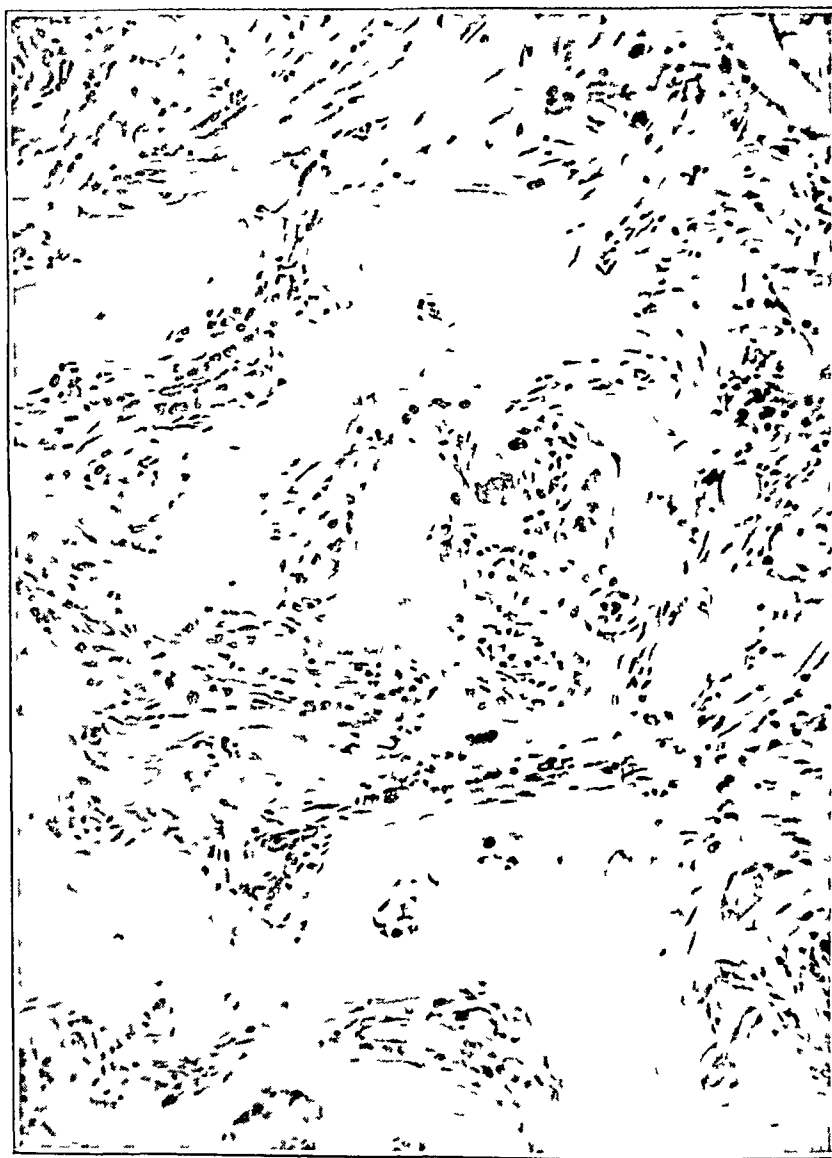


Fig. 7 (case 16)—Sternal marrow showing fibrosis, thickening of the trabeculae and numerous megakaryocytes

listless, florid and always tired. When 20 years old she had vertigo, headaches and diffuse body aches associated with splenomegaly and an 11,000,000 red blood cell count. Her family physician made the diagnosis of polycythemia (1909). For thirteen years the patient was treated with benzene and roentgen therapy, which controlled her symptoms. For the next ten years she complained constantly of fatigue. The red blood cell count remained within high normal limits until 1935. Three years before the patient's admission (1935) daily chills and fever developed, the origin of which could not be determined. The patient was admitted because of these unexplained episodes of three years' duration and for determination of the cause of the gradual drop in hemoglobin which accompanied them. This case was reported by Rosenthal and Bassen.<sup>17c</sup>

to obtain marrow on aspiration in the presence of a leukemic blood picture, should lead one to suspect a fibrotic change in the marrow. This finding led to the diagnosis of myelofibrosis in a case reported by Mavros in 1931. The performance of sternal puncture as a routine measure in all cases of anemia (leukoerythroblastic or otherwise), splenomegaly and leukemia has been responsible for the more frequent detection of myelofibrosis (Vogel, Erf and Rosenthal<sup>24</sup>).

**3 Sternal Biopsy**—Sternal puncture is the first step in identification, but biopsy of the sternal bone and marrow is important for conclusive evidence of the underlying myelofibrosis. Of the 17 cases reported in this communication, the diagnosis of myelofibrosis was made in 13 during life and in 4 at autopsy. Likewise, diagnosis of the condition was made during life by the following investigators: Chapman<sup>10</sup> in 2 cases, Fairbank<sup>20</sup> in 1 case, Stephens and Bredeck<sup>25</sup> in 2 cases and Thompson and Illyne<sup>26</sup> in 5 cases.

**4 Splenic Puncture**—Splenic puncture has been suggested by Hirschfeld<sup>17b</sup> and Weil<sup>27</sup> as a means of revealing the myeloid metaplasia which is usually found in myelofibrosis. This was performed in 3 recent cases and revealed the presence of numerous immature cells of both the myeloid and the erythroblastic series. Megakaryocytes were present to a varying degree. In some 27 reported cases reviewed by Hickling,<sup>28</sup> splenectomy was performed without any improvement in the general condition. In some instances numerous megakaryocytes were found in the spleen, leading to the idea of megakaryocytic leukemia. In some of these cases the disease may possibly have been associated with marked hyperplasia of the bone marrow—panmyelosis (Hickling<sup>28</sup>). In other instances, however, this megakaryocytic splenomegaly was associated with fibrosis of various degrees of the marrow as in the cases of Schwarz,<sup>29</sup> Donhauser,<sup>30</sup> Hewer,<sup>31</sup> Downey and Nordland<sup>27a</sup> and Carpenter and Flory.<sup>12</sup> For this reason it might be considered that the picture in some of these cases conforms to the changes observed in osteosclerotic anemia and that the increase of megakaryocytes in the spleen is a sign of active hemopoiesis or myeloid metaplasia.

**5 Lymph Node Puncture**—This was performed in 1 case and revealed a myeloid metaplasia, few megakaryocytes and erythroblasts and many immature myeloid cells scattered among the lymphoid cells. A biopsy of the lymph node also showed a myeloid metaplasia.

**6 Roentgen Studies**—A study of the bones is important for confirmatory diagnosis in all cases of osteopetrosis. About 50 per cent of patients with myelofibrosis show on roentgen examination mottled rarefactions or irregular condensations in the cortical portions of the bones and splintering or elevations of the

24 Vogel, P., Erf, L. A., and Rosenthal, N. Hematological Observations on Bone Marrow Obtained by Sternal Puncture, *Am J Clin Path* **7** 436 and 498, 1937.

25 Stephens, D. J., and Bredeck, J. F. Aleukemic Myelosis with Osteosclerosis, *Ann Int Med* **6** 1087, 1933.

26 Thompson, W. P., and Illyne, C. A. Clinical and Hematological Picture Resulting from Bone Marrow Replacement, *M Clin North America* **24** 841, 1940.

27 Weil, P. E., Isch-Wall, P., and Perlès, S. La ponction de la rate, Paris, Masson & Cie, 1936.

28 Hickling, R. A. Chronic Non-Leukemic Myelosis, *Quart J Med* **6** 253, 1937.

29 Schwarz, E. Ein Fall von Leukämie mit Riesenzellenemboli und Osteosklerose, *Ztschr f Heilk* **22** 294, 1901.

30 Donhauser, J. L. The Human Spleen as an Hematoplastic Organ, as Exemplified in a Case of Splenomegaly with Sclerosis of the Bone Marrow, *J Exper Med* **10** 559, 1908.

31 Hewer, T. F. Megakaryocytic Myelosis with Osteosclerosis, *J Path & Bact* **45** 383, 1937.

latter the hemopoietic tissue is replaced by various degrees of fibrosis. Ischemia of marrow may well be a factor in the development of the hematologic picture in each of these diseases, as it has been shown by Huggins and Wiese<sup>21</sup> that destruction of the nutrient vessels of bones may result in fibrosis of the marrow. According to Kistler,<sup>22</sup> such experimental production of fibrosis is difficult at times.

These conditions have been classified by Vaughan<sup>10</sup> under leukoerythroblastic anemia. This is defined as an anemia not necessarily very severe, characterized by the presence of a few immature white cells of the myeloid series and immature red cells in the peripheral blood. The recognition of this type of anemia during a routine examination of the blood may be the first indication of the existence of some unusual involvement of the bone marrow such as (1) carcinomatosis with skeletal metastases, (2) myelomatosis, (3) osteosclerosis, including (a) marble bone disease and (b) myelosclerosis, and (4) Cooley's anemia. With these conditions Vaughan<sup>11</sup> now includes polycythemia vera. A similar anemia was observed by us in association with lipomatosis of the bone marrow.

These conditions may then be recognized, in addition to study of the blood picture, by means of sternal puncture, sternal biopsy, splenic puncture, puncture of lymph nodes and roentgenograms of the bones.

*1 The Blood Picture*—The anemia may vary from a hypochromic to a hyperchromic type. The red cells, however, show anisocytosis and poikilocytosis. In the anemic, or "spent," stage of polycythemia and occasionally in primary myelosclerosis (possibly asymptomatic polycythemia), many elliptic red cells are present. Normoblasts are found except in rare cases. The blood platelets show pronounced variations. They may be either normal or much reduced in number in the peripheral blood. They also exhibit morphologic variations which are found almost exclusively in myelosclerosis. Some are particularly large, staining with a pale chromomere and pale-staining hyalomere.<sup>23</sup> Giant platelets and megakaryocytic fragments and megakaryoblasts are occasionally found. More marked and bizarre variations have been found after splenectomy by Downey and Nordland.<sup>23a</sup> Likewise, the white blood cells vary in number and type, leukopenia is most often found. It is not unusual to see a pronounced increase in nonsegmented neutrophils and occasionally a few myelocytes and an occasional myeloblast. The myelocytes and occasional myeloblasts may be associated with severe leukocytosis (leukocytopenia), as in 4 cases of this series.

*2 Sternal Puncture*—This is of primary importance in diagnosis. The density of the sternal bone may be detected by this means. In cases of osteopetrosis the bone is stony and the needle will not penetrate through the cortex, this situation suggesting the diagnosis immediately, especially if it occurs in an infant. The sternal bone in cases of "spent" polycythemia is also dense and yields little marrow. Smears of the marrow reveal only a few cellular elements. The sternal puncture in most cases of myelofibrosis is disappointing. The bone feels gritty on puncture and yields little marrow. In a few cases in which an appreciable amount was aspirated the nucleated cell count was less than that of the peripheral blood. The differential count on the smears showed a normal distribution of leukocytic and erythroblastic elements. The finding of a nonleukemic bone marrow, or failure

21 Huggins, C, and Wiese, E. Effect on Bone Marrow of Disruption of Nutrient Artery and Vein, *Ann Surg* **110** 940, 1939.

22 Kistler, G. H. Sequences of Experimental Infarction of the Femur in Rabbits, *Arch Surg* **29** 589 (Oct) 1934.

23 (a) Downey, H, and Nordland, M. Myeloid Megakaryocytic Hepato-Splenomegaly. *Folia haemat* **62** 1, 1939. (b) Rosenthal<sup>20</sup>

is less leukemoid. It is felt that there is a reciprocal functional relation between the liver and the spleen on the one hand, and the bone marrow, on the other. Normally during fetal life the liver and spleen are hyperfunctioning, while during adult life the bone marrow is the fundamental hematogenetic organ. The degeneration or disappearance of the cells of the bone marrow in myelofibrosis may be due to some reversal of this reciprocal relationship.

This situation is forcibly illustrated by the terminal fibrosis which occurs in polycythemia. The hyperplastic marrow in this disease shows a gradual change over a span of years to one of hypoplasia and generalized myelofibrosis. As these develop there is a gradual increase in the size of the liver and, especially, of the spleen which usually occupies during the terminal stage the whole left side and part of the right side of the abdomen. As in the primary type of myelofibrosis, there are severe anemia and a leukemoid blood picture.

Vaughan and Harrison<sup>11</sup> and Carpenter and Flory<sup>12</sup> stated the belief that the condition is due to a progressive hyperplasia of multipotential mesenchymal tissues by an unknown stimulus.

#### TREATMENT

The treatment of both osteopetrosis and myelofibrosis has been most unsatisfactory. Transfusions have proved to be of only temporary benefit to patients with the chronic types of these disorders. Splenectomy is contraindicated and has not proved of value in the few cases reported.<sup>11</sup> However, recent experimental work has brought new hopes for a treatment of myelofibrosis. Pfeiffer and Gardner<sup>10</sup> showed that estrogeneic substances administered in large amounts cause endosteal thickening and fibrosis of the marrow of mice, rats, pigeons and chickens, and they have been able to prevent the experimentally produced disease by the administration of testosterone propionate. Silberberg and Silberberg<sup>12</sup> noted that estrogeneic substances administered to immature guinea pigs accelerated the development of the mesenchymal reticulum of bone marrow toward fibrosis, bone formation and megakaryocytosis. Patient 16 was treated with testosterone propionate in an endeavor to inhibit a possible abnormal hyperestrogeneic activity. Although there was some hematologic and clinical improvement for a few months after the administration of the glandular substance the myelofibrotic process had progressed so far as to prevent critical evaluation of the efficacy of the treatment.

#### SUMMARY AND CONCLUSIONS

The clinical and laboratory observations in 1 case of osteopetrosis and 17 cases of myelofibrosis are discussed.

These conditions may be differentiated from refractory types of anemia, splenomegaly and leukemia by sternal puncture and, conclusively, by sternal biopsy.

Suggestive roentgenologic changes of the bones may be revealed in 33 per cent of the cases.

A practical classification of osteopetrosis and myelofibrosis is presented.

51 East Ninetieth Street

44 Carpenter and Flory<sup>12</sup> Downey and Nordland<sup>21</sup> Hirsch<sup>17a</sup>

periosteum<sup>32</sup> Von Jaksch<sup>33</sup> in 1901 was the first to demonstrate these changes. Some authors<sup>34</sup> described roentgenologic changes of the bones in their cases, while others<sup>35</sup> presented cases in which roentgen ray changes of the osseous system were not evident. Although in some cases the fibrosis extends from the endosteum to the periosteum, fractures rarely occur.

#### PATHOGENESIS

The cause of myelofibrosis is unknown. Some authors have suggested that the fibrosis is an aftermath or healing process of leukemia (Neumann,<sup>36</sup> Stephens and Bredeck,<sup>25</sup> Schwarz<sup>29</sup> and Lehdorff and Zak<sup>37</sup>). This is rather doubtful, as the bone marrow even in the earliest stages of myelofibrosis is hypoplastic except in polycythemia and does not show any changes typical of leukemia. Furthermore the characteristic pathologic changes of leukemia are missing. Hammer,<sup>38</sup> Askanazy<sup>39</sup> and Wade<sup>40</sup> associated myelofibrosis with pseudoleukemia, a condition subject to great controversy. A toxic agent has also been held responsible for the development of the fibrosis (Schmidt,<sup>35b</sup> Donhauser<sup>30</sup> and Wolf<sup>31</sup>). Lehdorff and Zak<sup>37</sup> and Anagnostu<sup>41</sup> thought the process one of atrophy of the marrow probably due to endogenous or exogenous agents, and recently Pfeiffer and Gardner<sup>19</sup> have demonstrated that estrogenic substances administered in large amounts cause endosteal thickening and fibrosis of the marrow in mice, rats, pigeons and chickens. Silberberg and Silberberg<sup>42</sup> have demonstrated similar changes in immature guinea pigs and Sutro<sup>43</sup> in mice after administration of estrogenic agents.

It seems more plausible, however, that the myeloid metaplasia of the liver and spleen is secondary or compensatory to the loss of marrow function. To some extent the enlargement of the liver and spleen parallels the degree of the fibrosis. The examination of the sternal marrow in the early stages revealed only partial fibrosis, and this was accompanied with a moderate enlargement of the spleen and with less severe clinical symptoms. In cases of chronic, long-standing involvement, from ten to seventeen years in our series, the spleen was greatly enlarged. In cases of acute myelofibrosis, in which this compensatory enlargement of the spleen is not prominent, the symptoms are more severe and the peripheral blood

32 Overgaard, K. Ein Fall von osteosklerotischer Anämie, *Acta radiol* **17** 51, 1936

33 von Jaksch, R. Multiple Periostaffektion und an myelogene Leukämie mahnender Blutbefund, *Prag med Wchnschr* **26** 2 and 19, 1901

34 Chapman<sup>10</sup> Fairbank<sup>3b</sup> Stephens and Bredeck<sup>25</sup>

35 (a) Mavros, A. Aleukamische, besser "nichtleukamische Myelose" mit Osteosclerosis, *Folia haemat* **43** 323, 1931 (b) Schmidt, M. B. Ueber osteosklerotische Anämie und Albers-Schonbergsche Krankheit, *Beitr z path Anat u z allg Path* **77** 158, 1927

36 Neumann, E. Ueber leukamische Knochenaffektionen, *Berl klin Wchnschr* **17** 281, 1880

37 Lehdorff, H., and Zak, E. Myeloide Leukämie im Greisenalter mit eigenartigen histologischen Befunden, *Folia haemat* **4** 636, 1907

38 Hammer, H. Primäre sarcomatöse Ostitis mit chronischen Rückfallsfieber, *Virchows Arch f path Anat* **137** 280, 1894

39 Askanazy, M. Ueber extrauterine Bildung von Blutzellen in der Leber, *Verhandl d deutsch path Gesellsch* **7** 58, 1904

40 Wade, H. W. A Preliminary Report on a Case of Hemopoietic Splenomegaly with Marrow Sclerosis, *J Philippine Islands M A* **1** 143, 1921

41 Anagnostu, J. L. Beitrag zum Studium der systematischen Osteosklerosen (Knochenmarksklerose mit leukamoiden Blutbilde), *Folia haemat* **50** 70, 1933

42 Silberberg, M., and Silberberg, R. Action of Estrogens on Skeletal Tissues of Immature Guinea Pigs, *Arch Path* **28** 340 (Sept) 1939

43 Sutro, C. Effects of Subcutaneous Injection of Estrogen upon Skeleton in Immature Mice, *Proc Soc Exper Biol & Med* **44** 151, 1940

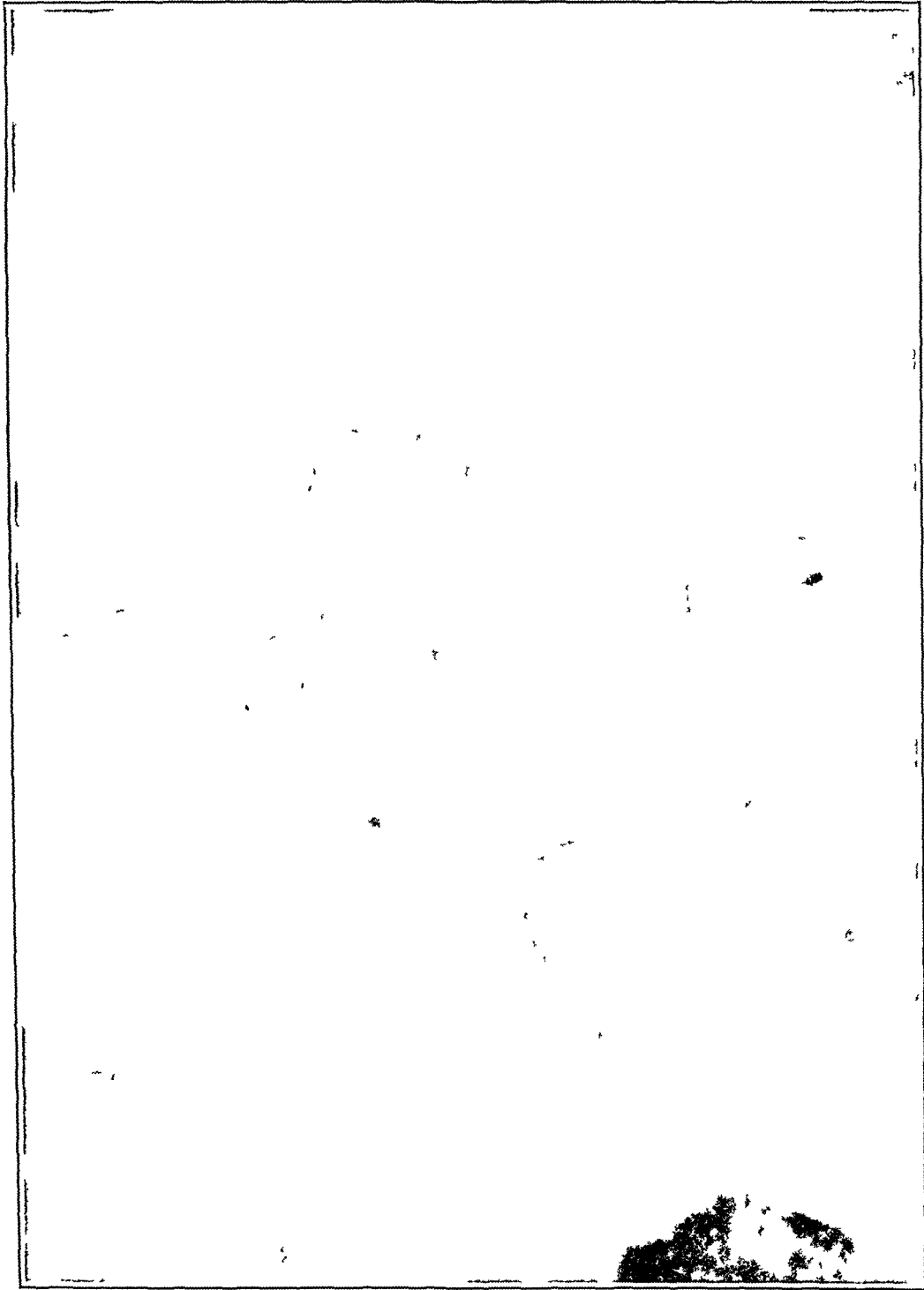


Fig 1—Photomicrographs of normal erythrocytes in human blood smear, printed in the usual manner

# PROFILE PRINTING IN THE PHOTOMICROGRAPHY OF BLOOD CELLS

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AND

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Photomicrography has been used to good advantage for a number of years to record for future reference or for purposes of demonstration the microscopic appearance of blood cells or tissue sections. That it might be used to demonstrate the actual shape of the erythrocyte and the location of granules in the leukocyte seemed possible, particularly after the introduction of the profile or three dimensional method of printing.

The problem which offered the most important possibility was that of demonstrating the spherocytes in the blood of a person suspected of having familial hemolytic anemia. However, in order to do this, it seemed desirable to visualize for comparison the erythrocytes of the blood of normal persons and those with other varieties of anemia.

In figure 1 is shown the photomicrograph of erythrocytes from a normal person as printed in the usual manner for comparison with the same erythrocytes recorded by the profile method, as in figure 2. The biconcave disk shape of normal erythrocytes is well illustrated in the latter. It is also to be noted that the concavity is of rather uniform depth in normal erythrocytes and occupies a rather fixed portion of the cell, leaving a border ring of uniform width and thickness.

The erythrocytes of a patient with hypochromic anemia, as seen in figure 3, show in addition to the characteristic variation in size and shape a concavity of varying depth and extent with a border ring of less than normal thickness. These evidences of insufficient hemoglobin to fill the cells properly are definitely more striking than those in the usual photomicrograph.

The erythrocytes in the blood of the patient with pernicious anemia, as seen in figure 4, show considerable variation in the extent and the depth of the concavity, although the border ring is generally of the same thickness as that of normal blood. In regard to this condition the profile printing has added little of importance to the ordinary photomicrograph but does emphasize the well known fact that the majority of the individual erythrocytes in pernicious anemia are well filled with hemoglobin.

The most striking difference in the photomicrographs prepared by the two methods is found in those of blood from a patient with familial hemolytic anemia. The erythrocytes are shown by the usual method in figure 5 and by the profile method in figure 6. In the latter the so-called spherocytes are seen as slightly convex disks or pill boxes with slightly expanded sides. These are not spheres as the term spherocyte suggests, but because of the definite convexity of their sides they are easily and certainly distinguishable from the biconcave disk of normal blood. Probably no method of demonstrating these cells so accurately or so certainly has been previously presented. This fact should indicate the value of this form of photomicrography as an aid to the diagnosis of familial hemolytic anemia.

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From the Medical Service of the Peter Bent Brigham Hospital

This article was presented as part of a scientific exhibit at the annual meeting of the Massachusetts Medical Society, May 21-22, 1940

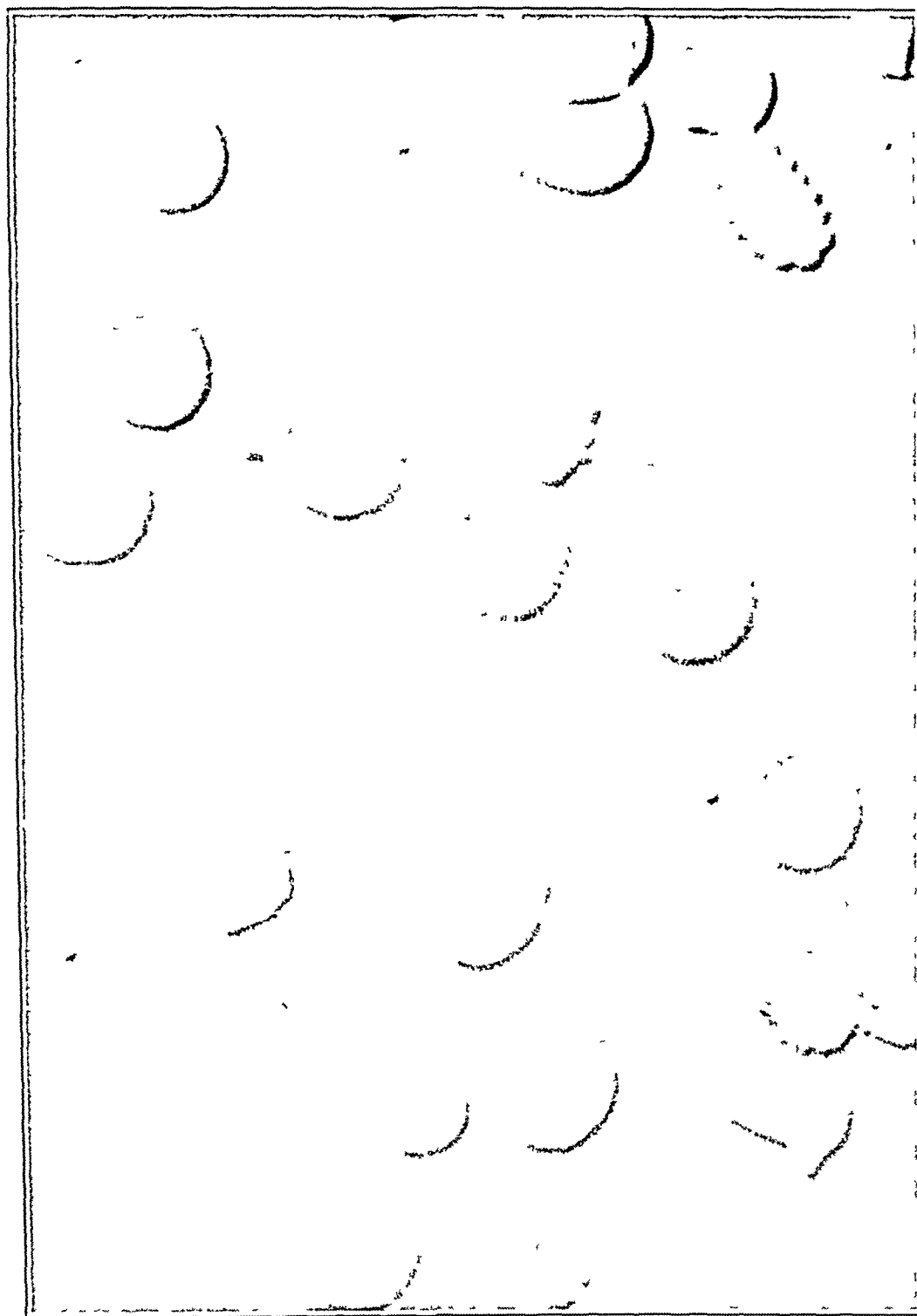


Fig 3—Profile of hypochromic anemia



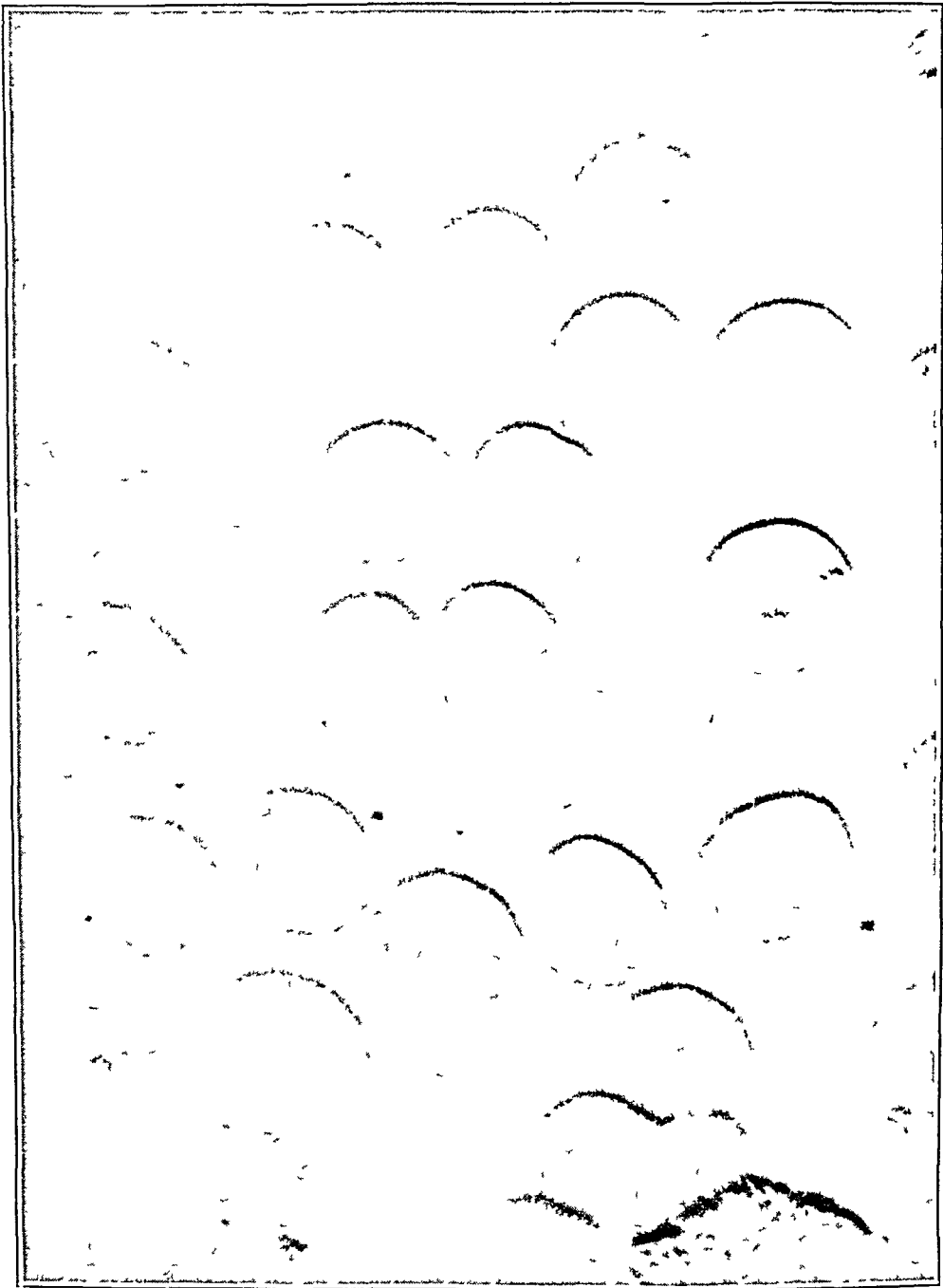


Fig 2—The erythrocytes shown in figure 1 as they appear in profile with the three-dimensional method of printing

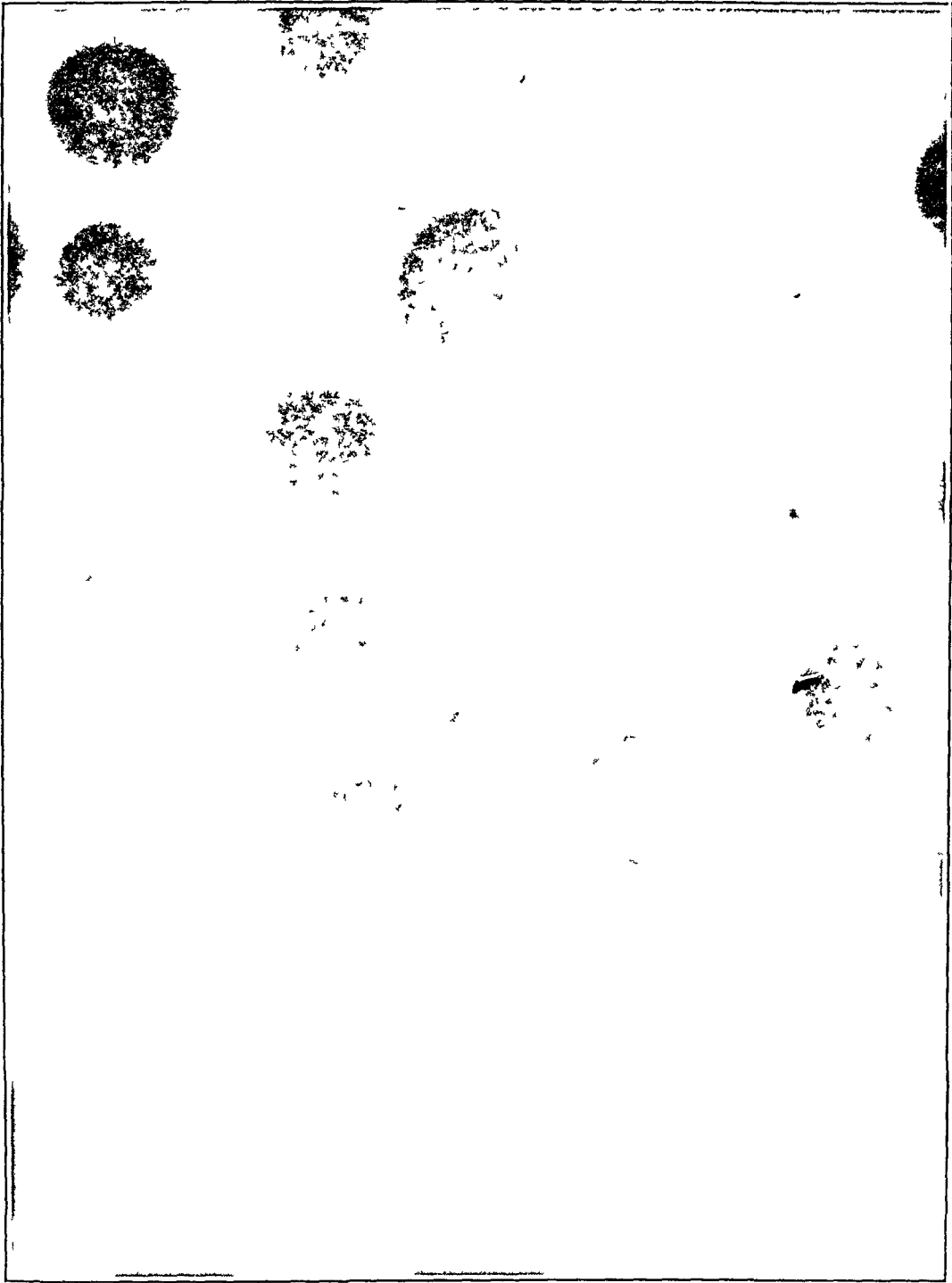


Fig 5—Hemolytic anemia



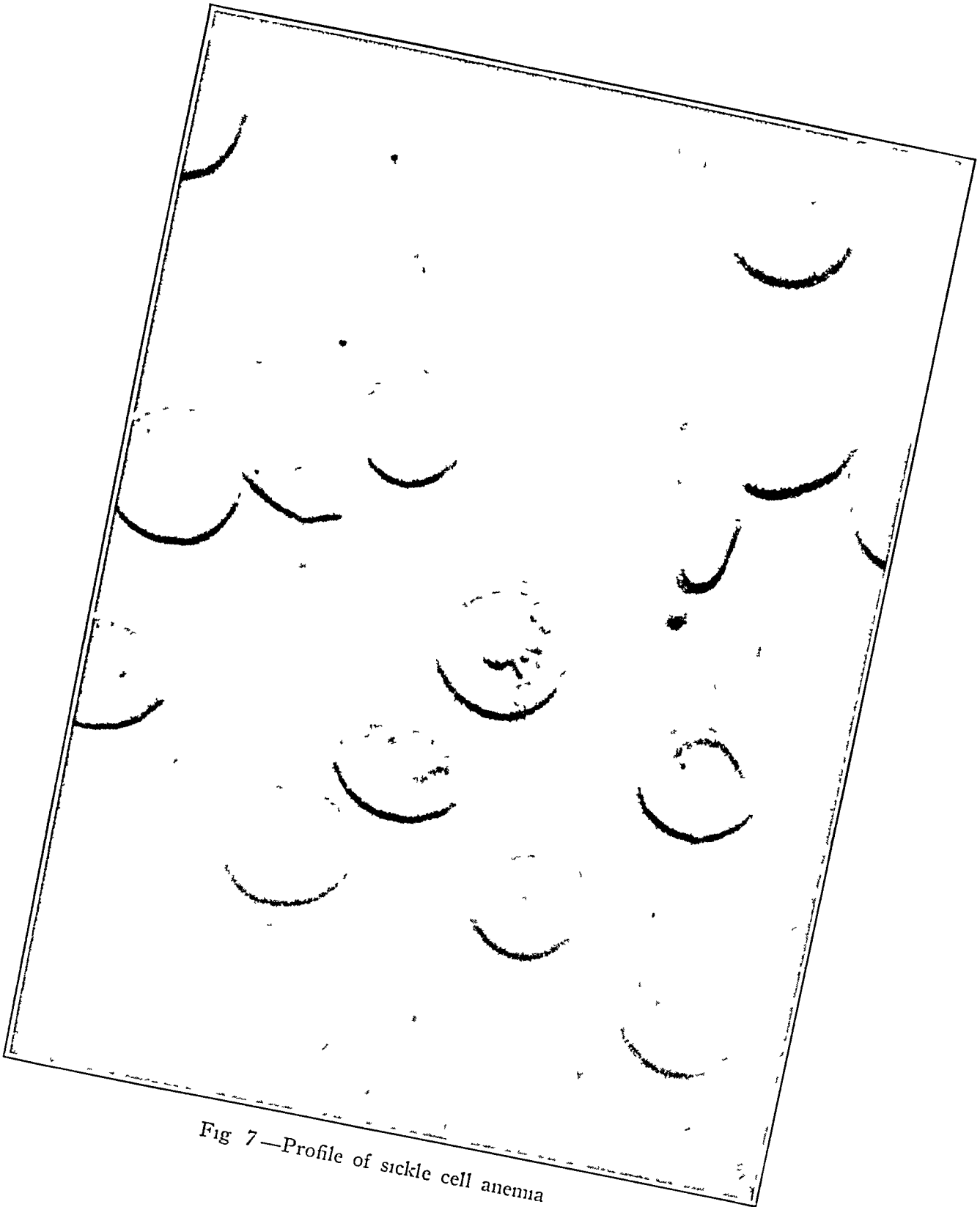


Fig 7—Profile of sickle cell anemia

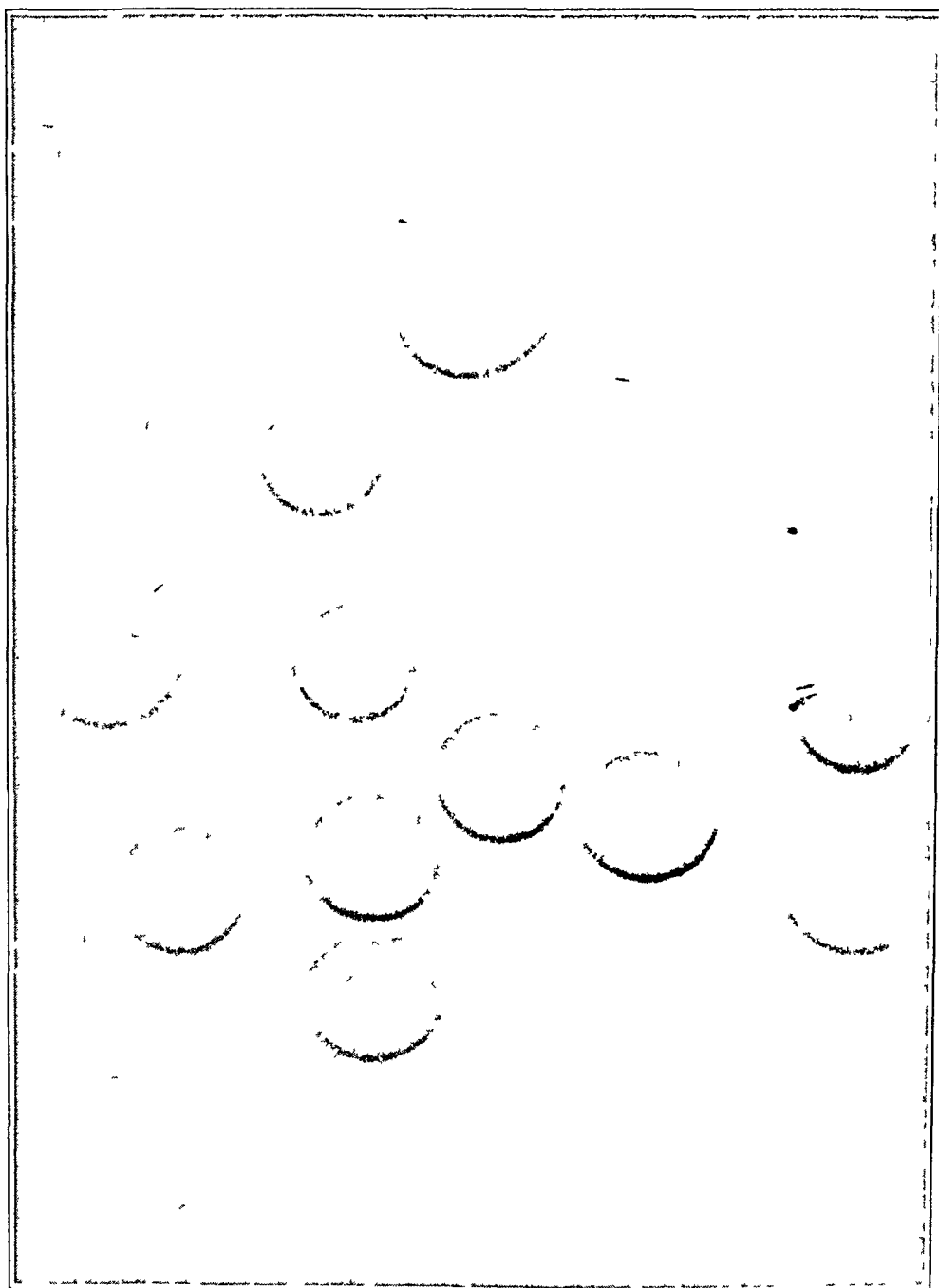


Fig 6—Profile of hemolytic anemia

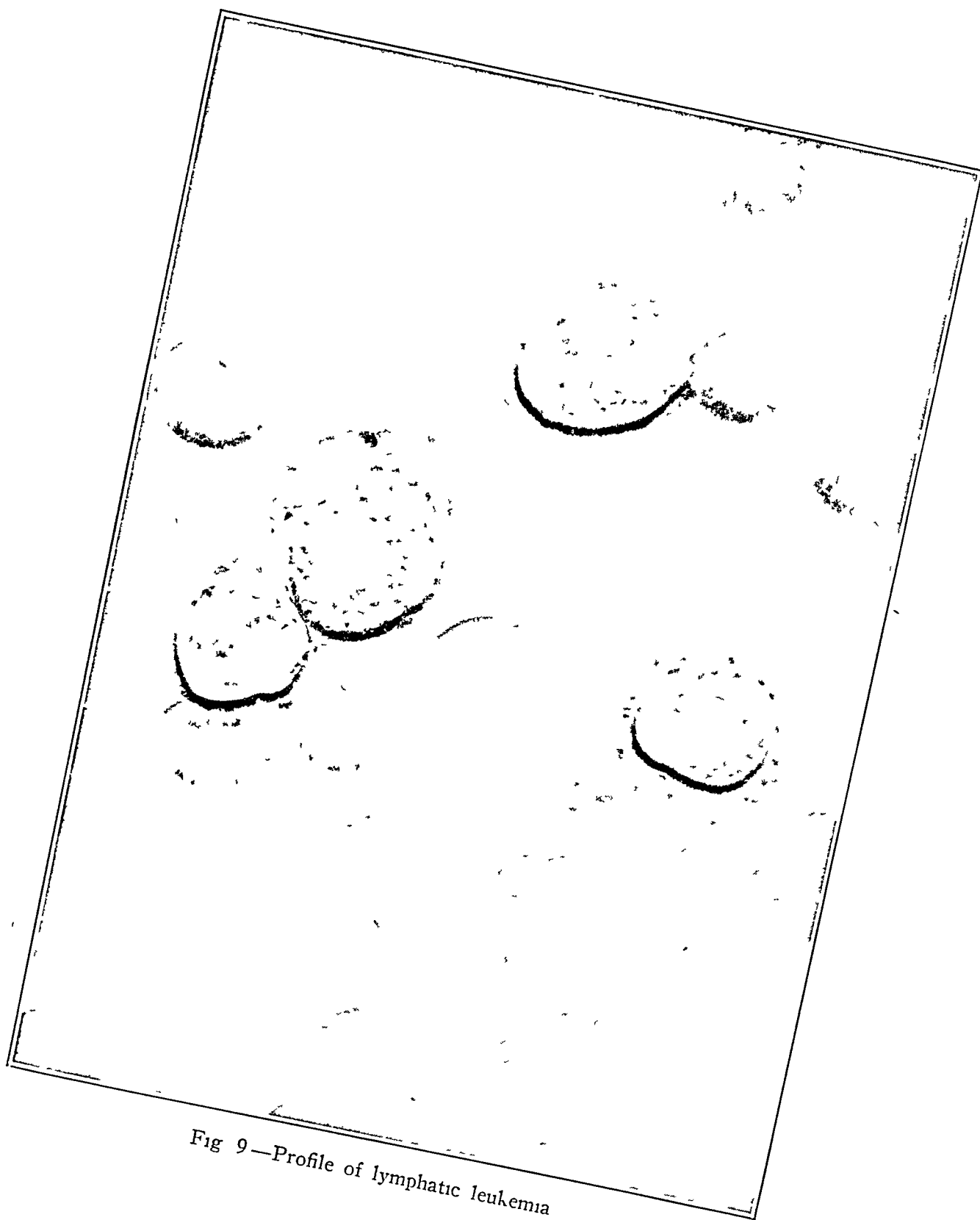


Fig 9—Profile of lymphatic leukemia

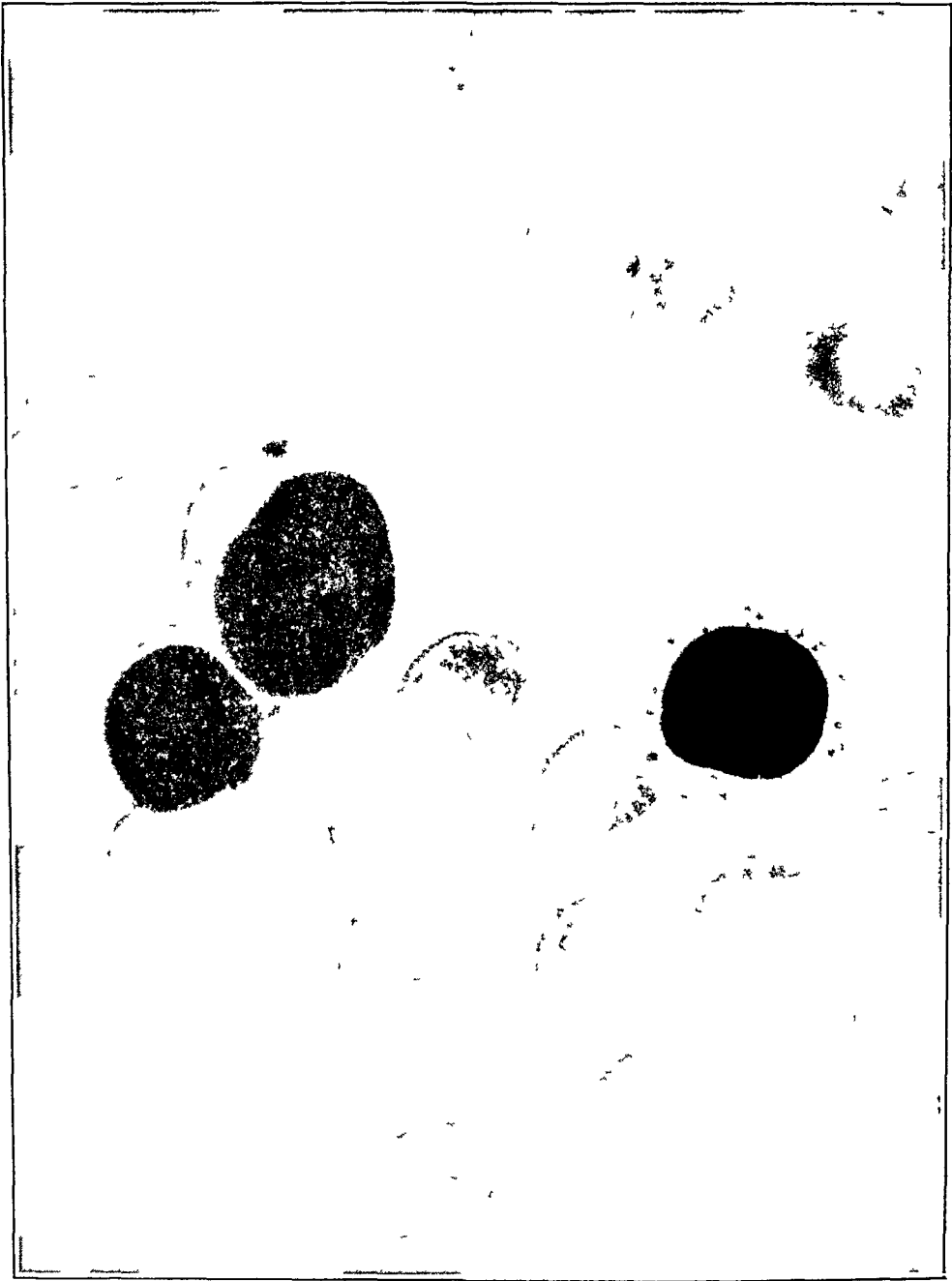


Fig 8—Lymphatic leukemia

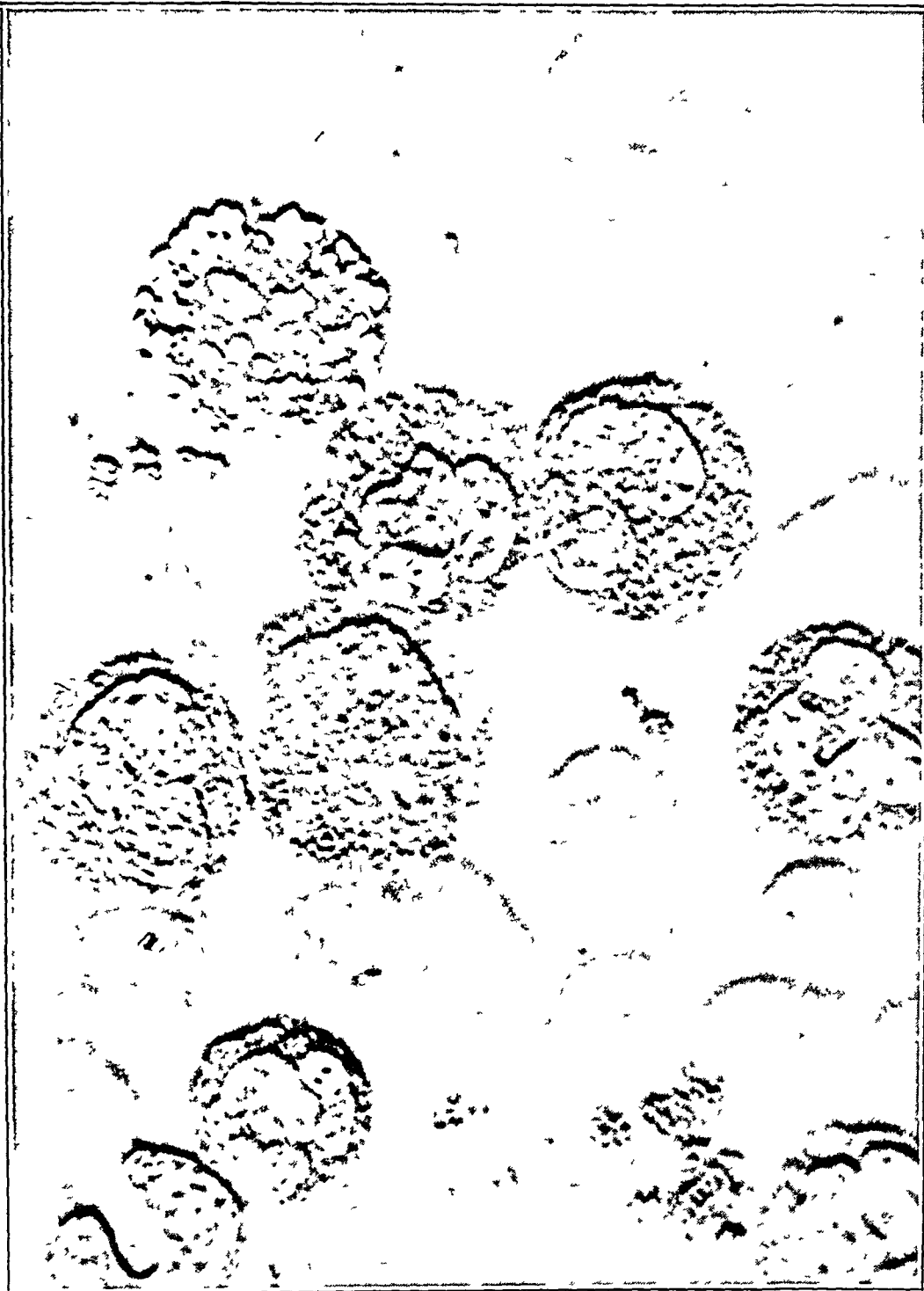


Fig 11 —Profile of myelogenous leukemia



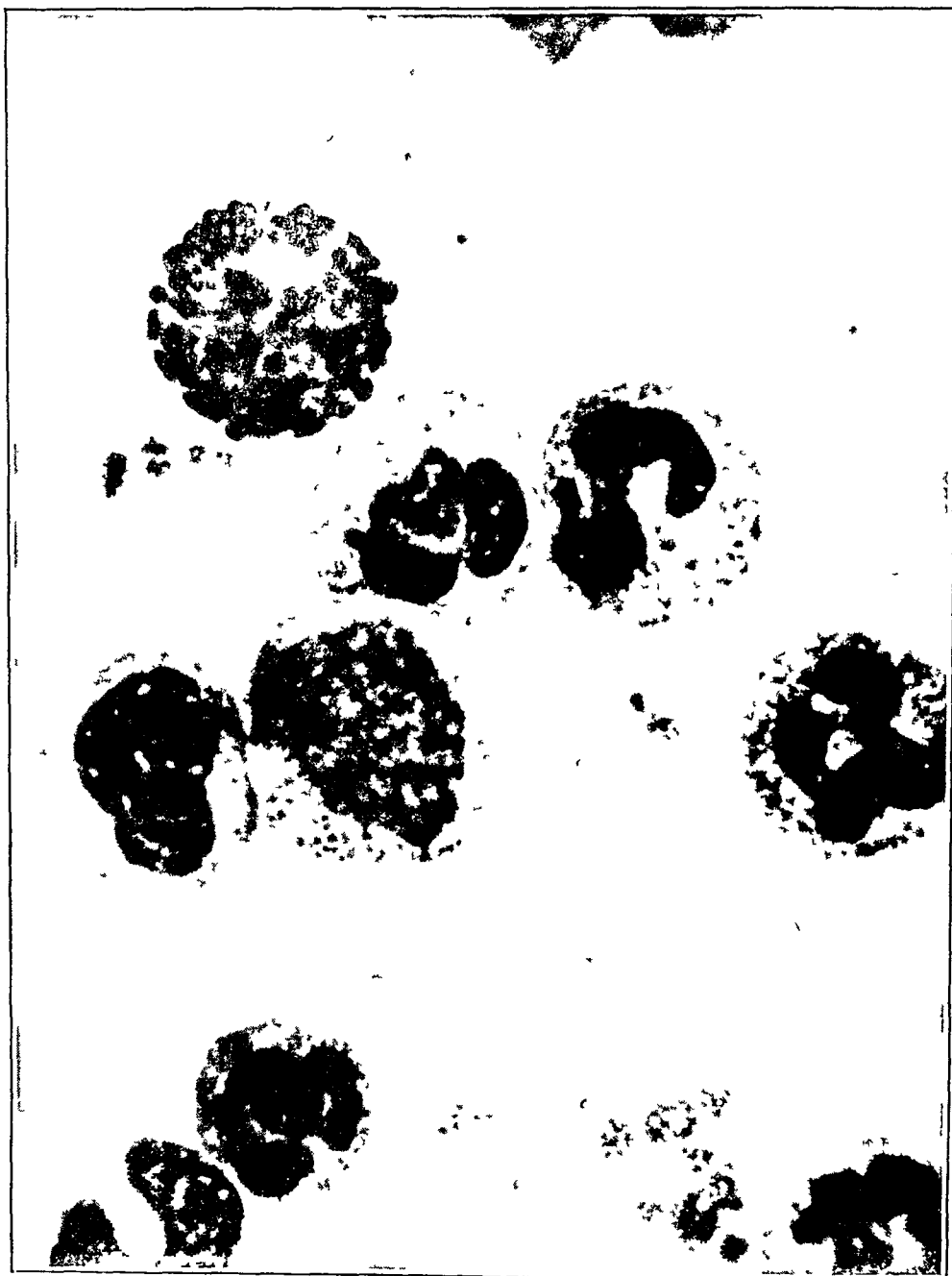


Fig 10—Myelogenous leukemia

# SIGNIFICANCE OF GLYCOSURIA

I ARTHUR MIRSKY, M D

AND

NORTON NELSON, PH D

CINCINNATI

Nearly three centuries ago Thomas Willis observed the urine from a diabetic patient to be "wonderfully sweet, as if imbued with honey or sugar" Ever since then glycosuria has been of paramount interest to the clinician, for it has become synonymous with diabetes mellitus However, glycosuria may be due to factors that have no relation to diabetes (e g, "renal glycosuria"), while, conversely, diabetes may exist in the aglycosuric patient (e g, in the presence of severe nephrosclerosis) Furthermore, there is a possibility that glycosuria alone is not an index of the severity of diabetes Hence, controversies exist in the literature concerning the significance of transient glycosuria, the significance of glycosuria associated with a normal blood sugar level and the relative importance of the blood sugar level as compared with the amount of sugar excreted in the urine

Recent studies in renal physiology have provided information that should clarify some of the misconceptions concerning the presence of dextrose in the urine This information resulted from the elaboration of Cushny's filtration-reabsorption theory of renal function and the application of newer principles to the problem of the excretion of dextrose Thus it is now known that the renal glomeruli filter the crystalloids of the blood into the tubules, where they are either reabsorbed or concentrated and subsequently excreted Accordingly, it is obvious that the excretion of dextrose must be dependent on three factors (a) the concentration of this substance in the arterial blood supply of the glomeruli, (b) the rate at which the glomeruli filter it out of the blood and (c) the rate at which dextrose filtered out is reabsorbed by the tubules Hence, before evaluating the significance of glycosuria in any case it is imperative to consider these three factors

## RENAL FACTORS

*Arterial Blood Sugar*—The factors that influence the arterial blood sugar and hence the capillary blood sugar are fairly well recognized Any phenomenon which causes a disturbance in the absorption of carbohydrates from the intestine, in their storage or in their utilization may influence the concentration of blood sugar Transient hyperglycemia may occur when carbohydrates are absorbed from the intestinal tract at an increased rate (e g, in hyperthyroidism<sup>1</sup>) or when there is a relative decrease in the rate of storage of carbohydrates in the liver (e g, in infections, hepatic damage or emotional excitement) Permanent hyperglycemia may occur in any condition in which there is a permanent excessive rate of glycogen breakdown in the liver or an insufficient rate of formation of hepatic glycogen (e g, in insulin insufficiency or in toxemia)

*Glomerular Filtration*—The glomerular filtrate is essentially the same as blood plasma in that it contains the various crystalloids of the blood in the same

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From the May Institute for Medical Research of the Jewish Hospital, and the Department of Biological Chemistry of the University of Cincinnati

1 Althausen, T L, and Stockholm, M Influence of the Thyroid Gland on Absorption in the Digestive Tract, *Am J Physiol* **123** 577, 1938

Figure 7 shows an interesting but not particularly important profile photomicrograph of the erythrocytes of a Negro boy with sickle cell anemia

Figures 8 and 9 contrast a usual photomicrograph of blood taken from a patient with chronic lymphogenous leukemia and a profile one of the same blood. It is interesting to note how the nuclei appear to be raised above the level of the cytoplasm, which has undoubtedly contracted over them in the dried, stained smear.

Perhaps the most striking if not the most important contrast between the two methods of printing is shown in figures 10 and 11. The beautiful design in the cells of the myeloid series, particularly in a basophil, in blood from a patient with chronic myelogenous leukemia is a most interesting example of the possibilities in the use of the profile photomicrograph for purposes of illustration and demonstration in hematology.

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The amount of dextrose that has been removed from the plasma per minute is represented by the product of the glomerular filtration rate (i.e., the inulin clearance or the urea clearance /0.6) and the concentration of dextrose in the plasma. Thus, at an arterial blood plasma sugar level of 80 mg per hundred cubic centimeters and a filtration rate of 125 cc of blood per minute, 100 mg of sugar will enter the tubules per minute (fig 1), at a blood sugar level of 220 mg per hundred cubic centimeters, 275 mg will enter the tubules per minute (fig 2). However, if the filtration rate drops because of glomerulonephritis, for example, to 50 cc per minute, then at the aforementioned blood sugar levels, only 40 mg (fig 4) and 110 mg (fig 5), respectively, will enter the tubules per minute.

*Tubular Reabsorption*—The amount of dextrose that is excreted in the urine is dependent on the balance between the amount of dextrose that enters the tubules

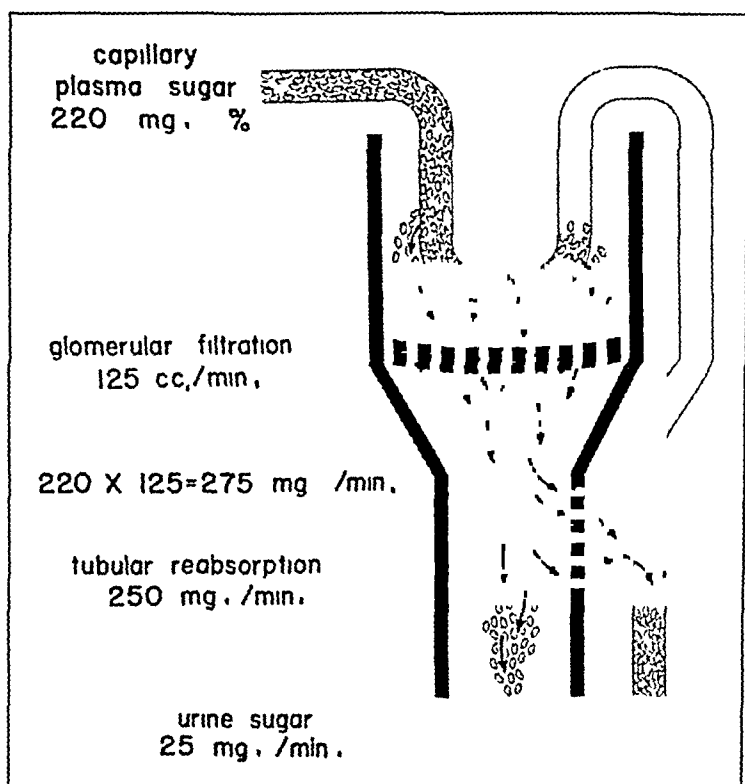


Fig 2—Diabetes mellitus. The dextrose filtration rate (plasma sugar  $\times$  filtration rate) exceeds the maximum reabsorptive capacity of the tubules because the plasma sugar is high

and the quantity that is transported by the tubules back into the blood stream. The studies of Shannon and Fisher<sup>3</sup> on normal dogs and those of Govaerts and Muller<sup>4</sup>

(inulin clearance = urea clearance /0.6 and parallel each other closely (Smith, H. W. Note on Interpretation of Clearance Methods in Diseased Kidney, *J Clin Investigation* **20** 631, 1941), one may employ the urea clearance to measure the rate of glomerular filtration (table) instead of using the more difficult inulin clearance procedure. Thus, if a patient has glycosuria, he is made to void at a specific hour, and a sample of blood is taken at the same time. After a definite interval he is made to void and another sample of blood is taken. The volume of urine passed during the interval is noted. Using the average value of the two blood samples, the volume of urine excreted per minute and the values for sugar and urea nitrogen in the urine, the formula  $UV/P$  is employed to determine both the urea and the dextrose clearance. Urea clearance /0.6 gives the glomerular filtration rate.

<sup>3</sup> Shannon, J. A., and Fisher, S. Renal Tubular Reabsorption of Glucose in Normal Dog, *Am J Physiol* **122** 765, 1938.

<sup>4</sup> Govaerts, P., and Muller, P. Mechanism of Glucose Excretion by Kidney in Diabetic Dogs, *J Clin Investigation* **18** 25, 1939.

concentrations as in the plasma. Thus, 100 cc of glomerular filtrate contains the same amount of dextrose as 100 cc of blood plasma. Therefore, the amount of sugar that enters the tubules is dependent on the ability of the glomeruli to filter this sugar from the blood. This ability is expressed as the "glomerular filtration rate." On the other hand, the amount of blood plasma which is entirely freed of dextrose in a given time is known as the "dextrose clearance." This represents the amount of sugar which has been filtered out by the glomeruli less that which has been reabsorbed by the tubules (fig 1). Obviously, in the aglycosuric person the dextrose clearance is zero. Hence, to measure the amount of dextrose which has passed through the glomeruli, it becomes necessary to measure the glomerular filtration rate, i. e., the rate at which the kidneys free the blood plasma of a substance which is neither reabsorbed nor secreted by the tubules. Inulin is such a substance, and the amount of blood which is entirely freed of inulin per minute is known as the "inulin clearance." Since all the inulin which has been filtered

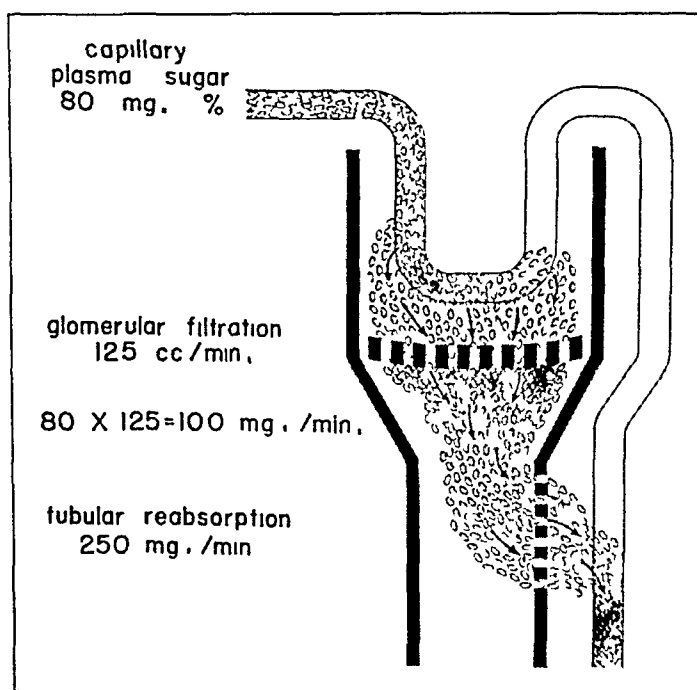


Fig 1—Normal. The reabsorptive capacity of the tubules exceeds the dextrose filtration rate (plasma sugar  $\times$  filtration rate)

into the tubules subsequently appears in the urine, the inulin clearance actually represents the rate of glomerular filtration not only of inulin but of any other solute present in the blood plasma. By such means it has been shown that about 125 cc of blood is normally freed of its crystalloids per minute. Any disturbance in the functional integrity of the glomeruli (e. g., glomerulonephritis or nephrosclerosis) will impair the filtration capacity and thereby reduce the amount of any solute (inulin, dextrose, urea) that normally can enter the tubules in a unit of time.<sup>2</sup>

<sup>2</sup> The clearance of any substance is expressed by the term  $UV/P$ , in which  $U$  and  $P$  represent the concentration of the substance in the urine and plasma, respectively, and  $V$ , the volume of urine excreted in a unit of time. For inulin  $UV/P = 125$  cc per minute. A substance like urea, which partially diffuses back into the blood stream, or a substance like dextrose, which is reabsorbed by the tubules (fig 1), will have a lower over-all clearance. Since the relation between the inulin clearance and the urea clearance is fairly constant

## RENAL THRESHOLD FOR DEXTROSE

It is apparent from the statements under "Tubular Reabsorption" that while the maximum reabsorptive capacity of the tubule is a basically independent function of the kidney, the threshold for the excretion of dextrose as it is ordinarily understood is not, but is dependent both on the maximum reabsorptive ability of the tubules and on the glomerular filtration rate. For example, with a given ability to reabsorb dextrose, loss of dextrose into the urine will occur whenever it is presented to the tubules more rapidly than it can be handled. Under normal conditions this does not occur because the amount of dextrose filtered out does not approach the maximum reabsorptive capacity of the tubules (fig 1). However, flooding of the tubules with dextrose may be produced in two ways:

1. A normal rate of glomerular filtration associated with a high concentration of dextrose in the filtrate (high blood sugar) will produce excretion of sugar (fig 2).
2. If the rate of glomerular filtration is abnormally high, loss of dextrose into the

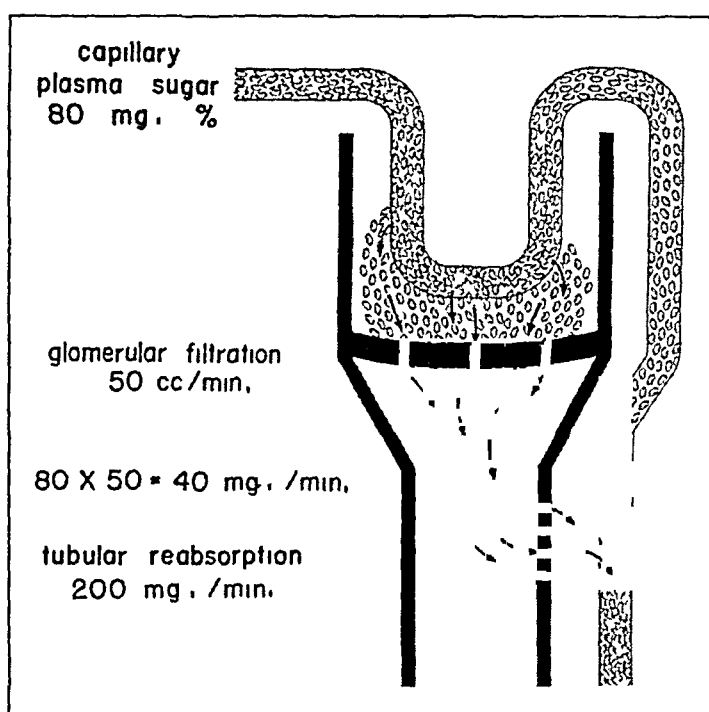


Fig 4—Glomerulonephritis. The reabsorptive capacity of the tubules exceeds the dextrose filtration rate (plasma sugar  $\times$  filtration rate) because of inadequate filtration through the abnormal glomerulus. The blood is not completely freed of dextrose at any time.

urine will occur at a normal or a low concentration of dextrose in the glomerular filtrate. Obviously the latter situation must be extremely rare, but the possibility of it may be revealed by future studies.

Conversely, excretion of sugar in the urine may occur at a normal concentration of dextrose if the reabsorptive capacity of the kidneys is abnormally low. This is the situation encountered in "renal glycosuria" (fig 3). Here the glomerular function is generally normal while the tubular ability to reabsorb dextrose is so impaired that glycosuria occurs at normal or only slightly elevated blood sugar concentrations.

The renal threshold for dextrose in man in the past has been determined by ascertaining the blood sugar level at which sugar appeared in the urine, the value obtained varied with whether the blood sugar was rising or falling. This procedure does not give a quantitative description of the actual physiologic mechanisms that are involved. Actually the renal threshold for sugar may be defined

on diabetic dogs led to the concept that the transfer of dextrose from the tubular urine to the blood (i.e., reabsorption) is accomplished by a mechanism which in its rate of transfer is independent of differences in concentration of sugar in the blood and the tubular urine. It is independent also of the rate of movement of either the tubular urine or the tubular blood supply, i.e., of glomerular filtration or of renal blood flow. The rate of the reabsorption of dextrose then becomes dependent on just two factors: (1) the availability of dextrose in the tubules and (2) the maximum capacity of the tubules to reabsorb dextrose.

As data have accumulated, the maximum reabsorptive capacity has been found to have a reasonably constant value during normal renal function.<sup>5</sup> This value is determined by measuring the amount of dextrose that enters the tubules (glomerular filtration rate  $\times$  plasma sugar concentration) less the amount which appears in the urine in the same interval of time. This estimation can be used as an index

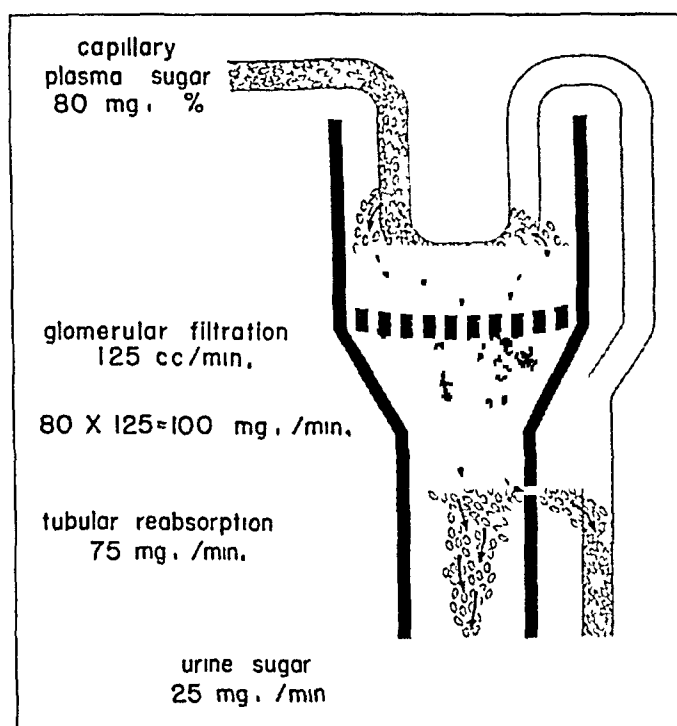


Fig. 3—"Renal glycosuria." The dextrose filtration rate (plasma sugar  $\times$  filtration rate) exceeds the maximum reabsorptive capacity of the tubules because of some physiologic, pharmacologic or pathologic deficiency of tubular function.

of the efficiency of one aspect of renal activity just as the glomerular clearance is used of another. In normal man the maximum reabsorptive capacity of the tubules has been found to vary from 250 to 350 mg. per minute.<sup>6</sup> When tubular function is impaired, the reabsorptive capacity of the tubules may be so reduced that dextrose will appear in the urine even at normal or low blood sugar levels (fig. 3).

5 Shannon, J. A. Kidney, in Luck, J. M., and Hall, V. E. Annual Review of Physiology, Stanford University, Calif., Annual Reviews, Inc., 1942, vol. 4, p. 297.

6 Nelson, N., and Mirsky, I. A. The Influence of Glomerular Filtration on the Glucose "Threshold" in Man, *Am. J. Physiol.* **129** P429, 1940. Steinitz, K. Studies on Conditions of Glucose Excretion in Man, *J. Clin. Investigation* **19** 299, 1940. Smith, H. W., Ranger, H. A., Chasis, H., and Goldring, W. The Dispersion of Glomerular Activity in the Normal and Hypertensive Kidney, *Am. J. Physiol.* **133** P450, 1941.

litus in patients with a history of "renal glycosuria" should be the same as it is in the general population

This view is completely borne out by our data on 3 patients with renal glycosuria (R T, W W and F W), who show normal glomerular function but marked reduction in dextrose reabsorbed (table). This reduction is of about the same order of magnitude in each patient, the maximum reabsorptive capacity of the tubules ranges from 75 to 97 mg per minute, in contrast to the normal ranges of from 250 to 350 mg per minute. The threshold (dextrose reabsorbed per hundred cubic centimeters of glomerular filtrate) is in each case definitely below the normal fasting sugar level.

Whereas it is possible to find persons suffering from renal glycosuria who may have metabolic disturbances as a result of the constant loss of sugar (1 e,

*Decreased Tubular Reabsorptive Ability in "Renal Glycosuria" and in Bright's Disease*

Patient	Period	Dextrose						
		Clearance		Blood, Mg per 100 Cc	Filtered Out of Blood (3) × (2), Mg per Min	Excreted, Mg per Min	Reab- sorbed (4) — (5), Mg per Min	Threshold (6) / (2), Mg Reab- sorbed per 100 Cc of Glomerular Filtrate
		Urea Clear- ance (1)	Urea Clear- ance/0.6 (2)					
R T	1		115*	82	95	19	75	67
	2		114	81	92	16	76	67
	3		115	80	92	15	77	67
	Average		115	81	93	17	76	66
F W	1		123	90	111	12	99	80
	2		112	88	99	9	90	80
	Average		118				95	80
W W	1	66	110	80	88	11	77	70
	2	57	95	81	77	10	67	71
	Average						72	71
M E	1	25	41	325	133	16	117	285
	2	25	42	307	129	15	114	271
	3	21	34	305	103	12	91	268
	4	19	32	303	97	10	87	272
	Average						103	276
L T	1	37	61	258	157	54	103	169
	2	41	67	226	151	43	108	161
	3	36	60	224	134	36	98	163
	Average						104	165

\* Inulin clearance, simultaneous urea clearance

relative starvation), there is no evidence of such difficulties in the 3 whose cases have been cited. There has been no evidence of starvation or ketosis in these cases, nor could any be anticipated from the magnitude of the loss of sugar occurring if a normally adequate dietary regimen was permitted. In these 3 persons with impaired tubular reabsorptive ability for dextrose no evidence of additional renal dysfunction was found, nor was there any history suggestive of a responsible factor in the origin of this condition. This situation is that encountered in the patient with true or idiopathic renal glycosuria.

A similar situation can be produced experimentally by the administration of phlorhizin, which inhibits the reabsorption of dextrose, presumably by inhibiting phosphorylation in the tubules,<sup>7</sup> and therefore the condition produced may be

<sup>7</sup> Rapoport, S., Nelson, N., Guest, G. M., and Mirsky, I. A. The Turnover of Acid-Soluble Phosphorus in the Kidneys of Rats, *Science* **93** 88, 1941



as that concentration of blood sugar at which the quantity entering the tubules per unit of time exceeds that which the tubules can reabsorb in the same interval of time. By measuring the rate of glomerular filtration of sugar and the rate at which sugar appears in the urine it is possible to evaluate the transfer of dextrose in the kidney and to assess its efficiency. Quantitatively, the threshold may be expressed by the value for "dextrose reabsorbed per hundred cubic centimeters of glomerular filtrate" (i. e., dextrose reabsorbed/glomerular filtration rate)

It is evident that, given a patient with glycosuria, the glomerular filtration rate will provide information concerning the amount of dextrose that entered the tubules whereas the dextrose clearance<sup>1</sup> will make possible the estimation of the amount of sugar reabsorbed, since the amount of dextrose filtered into the tubules less the amount of dextrose excreted equals the amount reabsorbed. In this manner it becomes possible to evaluate the significance of glycosuria in any case irrespective of the blood sugar level as well as of the status of renal function.

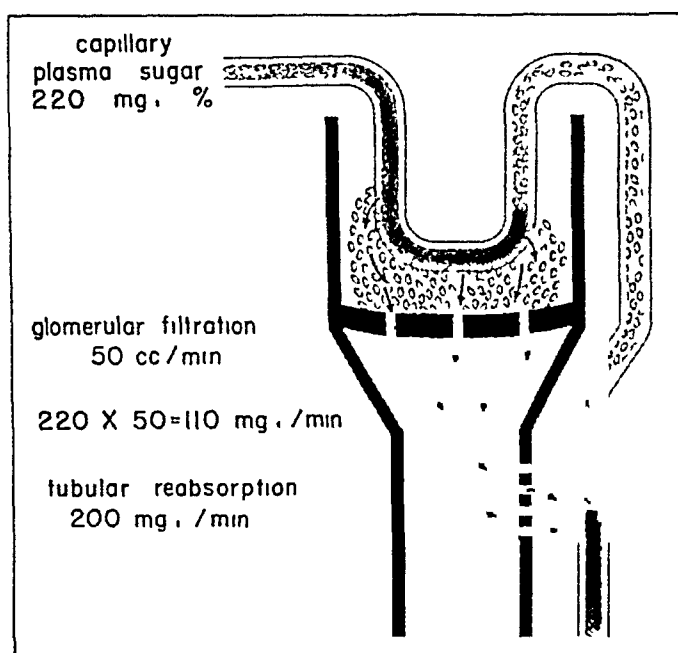


Fig 5—Diabetes and nephrosclerosis. The reabsorptive capacity of the tubules exceeds the dextrose filtration rate (plasma sugar  $\times$  filtration rate) because of inadequate filtration through the abnormal glomerulus.

*Renal Glycosuria*—This apparently benign abnormality in the renal control of dextrose excretion has been basically a well understood condition. However, the vagueness of the diagnostic criteria and the confusion of the condition with diabetes mellitus have unnecessarily complicated the detection and subsequently the handling of renal glycosuria. It is obvious that the term "renal glycosuria" should be reserved for those cases in which the excretion of dextrose in the urine is occasioned by an inefficient renal reabsorptive mechanism (fig 3). It is probable that this inefficiency results from a number of etiologic factors and should, therefore, be distinguished on the basis of these factors as physiologic, pathologic or pharmacologic in nature. Moreover, there is no reason why this same inefficiency in reabsorption of dextrose cannot be accompanied by other causes of glycosuria, such as the hyperglycemia of diabetes mellitus. That does not mean that there is any relation between them other than the fact that diabetes can occur in persons with normal or abnormal kidneys. In other words, the incidence of diabetes mel-

function and the consequent production of glycosuria does not necessarily have any metabolic significance if the loss of calories is adequately compensated

It is a common observation that the elderly patient with diabetes shows a 'decreased renal threshold' in that a high blood sugar level may be encountered without as great glycosuria as might be observed in a younger patient with diabetes. In fact, such elderly patients may be aglycosuric in spite of a high blood sugar level. This has led to much speculation concerning the severity of the diabetic syndrome in the elderly patient, the contention being that the lesser glycosuria indicates a milder disease. However, analysis by means of the procedures described in the preceding paragraphs reveals that the decreased glycosuria is due either to a decrease in glomerular filtration, consequent to pathologic changes in the glomeruli (fig 5), or to an increase in capacity to reabsorb dextrose, i. e., to a disturbance in renal function and not to some extrarenal metabolic factor. That the elderly diabetic person need not have a different threshold in comparison with the young diabetic person may be illustrated by the observation that a patient 14 years of age with a diabetic history of several years' duration had a renal threshold of 254 mg per hundred cubic centimeters, while another patient aged 60 years had a threshold of 257 mg, yet the child showed a much more severe clinical picture than did the elderly patient. The only conclusion that can be drawn from this illustration is that the kidneys function equally well in both but that the general metabolic disturbance is greater in the child. Hence, when the glycosuria is diminished in an elderly subject, it may merely reflect some pathologic change in the kidney.

#### SUMMARY

It is apparent that glycosuria reflects not only the metabolic phenomena which produce hyperglycemia but the physiologic status of various functional units of the kidney. Hence a proper appraisal of the significance of glycosuria necessitates determination of the rates of glomerular filtration and tubular reabsorption as well as of the concentration of blood sugar. In the normal person all three factors are normal (fig 1). In the patient with "renal glycosuria" or glycosuria induced with phlorhizin and probably in the patient with glycosuria of pregnancy the reabsorptive capacity is decreased (fig 3). In the patient with diabetes mellitus the blood sugar is high and the renal factors are normal (fig 2). In the aged person with diabetes and nephrosclerosis there may be a greater or lesser impairment of the functional units of the kidneys, which results in a decrease in the glomerular filtration rate and hence in an increase in the concentration of blood sugar required to produce glycosuria (figs 5 and 6).

Accordingly, the concentration of sugar in the urine, in itself, is not an index of the severity of the metabolic disturbance that may be present nor does it give any information concerning the prognosis. Only when the renal factors are properly evaluated does the amount of dextrose in the urine become significant. Then one can determine the amount of carbohydrate which the patient retains on a specific dietary intake and thereby arrive at a proper evaluation of the severity of the metabolic disorder.

The May Institute for Medical Research

regarded as a pharmacologic type of renal glycosuria. Here too no metabolic disturbance ensues so long as the patient eats an adequate amount of carbohydrate and thereby compensates for the loss in the urine.

*"Bright's Disease"*—In patients with various renal diseases one finds lowered tubular capacity to reabsorb dextrose similar in severity to that in patients with renal glycosuria. As data accumulate, it is probable that instances will be encountered in which a disease process of known genesis more or less specifically involves this tubular mechanism. Such cases would show continuous glycosuria of the same type as that found in cases of renal glycosuria. However, in each case of pathologically low tubular reabsorptive capacity which we have studied so far we have found glomerular dysfunction of sufficient magnitude to raise the threshold for sugar spillage to normal or nearly normal levels (fig 6).

Two examples of patients with Bright's disease (M. E. and L. T.) with this parallel injury to the tubules and the glomeruli are given in the table. It is apparent

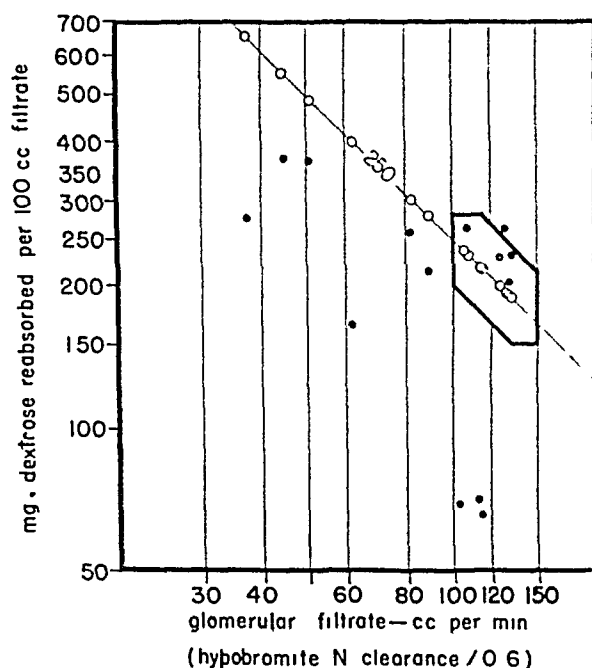


Fig 6—Glomerular filtration and renal threshold. The influence of glomerular filtration on the renal threshold for dextrose. The open circles indicate the theoretic reabsorptive capacity of the normal kidney. The black circles indicate the actual data obtained in various patients, showing that if the glomerular filtration is decreased there is also a tendency for the tubular reabsorption to decrease. When the latter does not decrease as much as the former, the threshold for dextrose is increased.

that neither of these persons would normally be apt to have glycosuria (fig 4). However, should the pathologic disturbance involve the tubules to a greater degree than the glomeruli, glycosuria would ensue. This has been observed occasionally in Bright's disease, in consequence of which the status of the patient's carbohydrate metabolism was questioned.<sup>8</sup> On the other hand, should the pathologic process involve the glomeruli of a patient with diabetes to a greater degree than it involves the renal tubules, glycosuria would decrease since less sugar would be filtered into the tubules (fig 5). It cannot be emphasized too often that a disturbance in renal

<sup>8</sup> Williams, J. R., and Humphreys, E. M. Clinical Significance of Blood Sugar in Nephritis and Other Diseases, Arch Int Med **23** 537 (May) 1919.

## REPORT OF A CASE

*History*—A 27 year old man was referred to the outpatient department of the Kings County Hospital in February 1939 by his private physician after he was found to have a positive Wassermann reaction. The patient attended the clinic regularly, was not granted any rest periods and by Feb 15, 1941 had received forty-nine injections of a bismuth compound and forty-four injections of mapharsen. On February 17 he fell and fractured his left femur. He was unable to return to the clinic until April 5, when 0.04 Gm of mapharsen was administered intravenously at 10 a. m. Two hours later, while at home, he was found having a generalized convulsion. He was admitted to the neurologic service of Dr. A. M. Rabiner, Kings County Hospital, approximately three and one-half hours after the injection.

On admission the patient was stuporous, had a dusky blue appearance and was breathing irregularly. The chest was clear and resonant. The heart tones were poor, and the rhythm was regular. The blood pressure was 80 systolic and 50 diastolic. The abdomen was soft, no organs were felt. There was bilateral pes cavus.

On neurologic examination the right pupil measured 3.5 mm, the left one 2.0 mm. Neither iris reacted to light. The eyes often deviated to the left. There were twitchings of the perioral group of muscles on the left side and chattering movements of the jaw. The deep

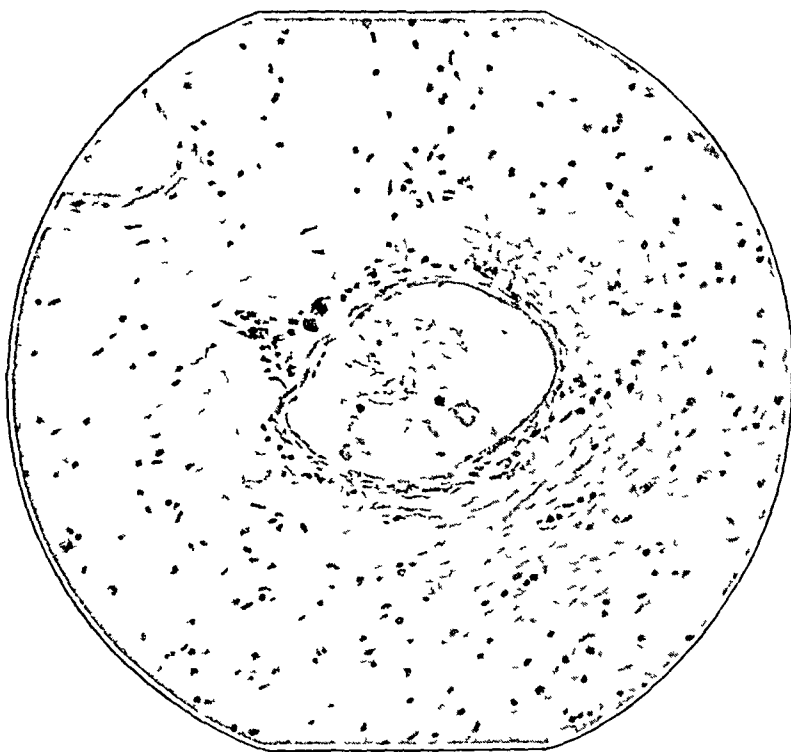


Fig 1—Perivascular necrosis. Several phagocytes loaded with hemosiderin can be seen. Hematoxylin and eosin, high magnification.

reflexes were decreased throughout, the superficial ones could not be elicited. There were bilateral Babinski responses of the toes. The patient did not respond to pin prick.

Shortly after admission the patient partially regained consciousness. The following day he could not void, and catheterization was required. Two days later hemiplegia, hemianesthesia and homonymous hemianopia developed, all on the left side.

Each day for twelve days, until April 17, the patient was observed in one or more convulsions. During a convulsion, consciousness was maintained, the head and eyes were turned to the left and there were clonic movements of the entire left side of the body. Occasionally, such movements were noted on the right side.

On April 18, the thirteenth day of hospitalization, the patient lapsed into a stuporous state. Failure to respond to ordinary measures and the predominance of unilateral signs suggested a localized lesion. The patient was then transferred to the neurosurgical service of Dr. E. Jefferson Browder. Ventriculographic studies revealed dilatation of both lateral ventricles and anomalous formation of the corpus callosum.

The patient did not regain consciousness. On April 22 twitchings of the right side of the mouth were noted. On that day, the patient's temperature rose to 105 F and death ensued, twenty-one days after admission.

# ENCEPHALOPATHY FOLLOWING MAPHARSEN THERAPY

## PATHOLOGIC REPORT WITH UNUSUAL FINDINGS

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N APTER M D

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Although mapharsen has been widely adopted in the treatment of syphilis since 1934, reports of fatalities from toxic effects following its use are few. In 1933 Cole and others<sup>1</sup> reported the first case of death attributed to mapharsen, acute nephrosis was the primary cause of death. Two years later Simon and Iglauer<sup>2</sup> reported a case in which a patient had died of anuria after five injections of mapharsen. Shortly afterward Rein and Wise<sup>3</sup> added 2 more cases with fatal outcome. In 1 of these aplastic anemia had developed in the other granulocytopenia. In 1941 Kirkham and Perlmutter<sup>4</sup> reported a case in which death was due to aplastic anemia following twenty injections of mapharsen.

The first report of mapharsen therapy followed by involvement of the central nervous system appeared in 1939 from India. Rajam and Rao<sup>5</sup> described a case in which hemorrhagic encephalitis followed the use of mapharsen. This complication occurred in a man aged 47 with primary syphilis and a positive serologic reaction for syphilis and followed the second injection of 0.04 Gm of mapharsen. The first injection had been given five days previously. Within twenty-four hours confusion, generalized rigidity, exaggerated tendon reflexes and extensor plantar responses developed. Death supervened in twenty-four hours. On gross examination "a full and engorged condition of the vessels of the surface of the brain" was noted. Results of microscopic examination were not reported.

A second case was recorded by Chargin<sup>6</sup> in 1940. A patient had received 12 Gm of mapharsen intravenously in five days by the continuous intravenous drip method. Two days after the completion of treatment, convulsive seizures developed and the patient lapsed into stupor. He responded to therapy and recovered in five days. The case presented here is the first in which histopathologic study of the brain was made.

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Presented at a meeting of the Brooklyn Neurological Society, Nov 25, 1941.

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1 Cole, H N, and others. Cooperative Clinical Studies in Treatment of Syphilis. Arsenical Reactions, *Ven Dis Inform* **14** 173, 1933.

2 Simon, S D, and Iglauer, A. Death Following Mapharsen Therapy, *Am J Syph, Gonorr & Ven Dis* **23** 612, 1939.

3 Rein, C R, and Wise, F. Mapharsen in the Treatment of Syphilis in Office Practice, *J A M A* **113** 1946 (Nov 25) 1939.

4 Kirkham, D, and Perlmutter, M. Fatal Aplastic Anemia Following Use of Mapharsen. Report of Case, *Arch Dermat & Syph* **43** 111 (Jan) 1941.

5 Rajam, R V, and Rao, N V. Mapharside in the Treatment of Syphilis. Clinical Study, *Indian M Gaz* **74** 24, 1939.

6 Chargin, L. Massive Arsenotherapy in Early Syphilis by Continuous Intravenous Drip Method. Toxicologic Manifestations, *Arch Dermat & Syph* **42** 248 (Aug) 1940.

vascular spaces. Petechial hemorrhages were seen in scattered parts of the brain, principally in the gray matter. Small and medium-sized arteries in the cortex, white matter and basal ganglia were surrounded by rarefied zones of necrosis. The rarefied zones contained macrophages distended with hemosiderin. They appeared to be the remains of previous minute perivascular hemorrhages.

Two types of degenerative lesions formed a distinctive part of the pathologic condition. The first was evident in the temporal lobe, where poorly circumscribed areas of degeneration involved the deepest layers of the cortex and extended parallel to the surface in a laminar fashion (fig 1). At times all cortical layers were included in the degenerative process. This pathologic process stopped sharply at the edge of the white matter. These lesions had a chaotic and disorganized aspect (fig 2). In them the ground substance was spongy, edematous and disintegrating. The normal layers of the cortex could not be made out. The ganglion cells had disappeared. There was considerable gliosis, the tissue consisting chiefly of plump, protoplasmic astrocytes. The blood vessels appeared normal.

A second type of degenerative lesion also occurred in the cortex but was smaller, more discrete and more localized (fig 3). Within these lesions ganglion cells and glia were absent. Nests of closely aggregated capillaries formed by the proliferation and dilatation of small

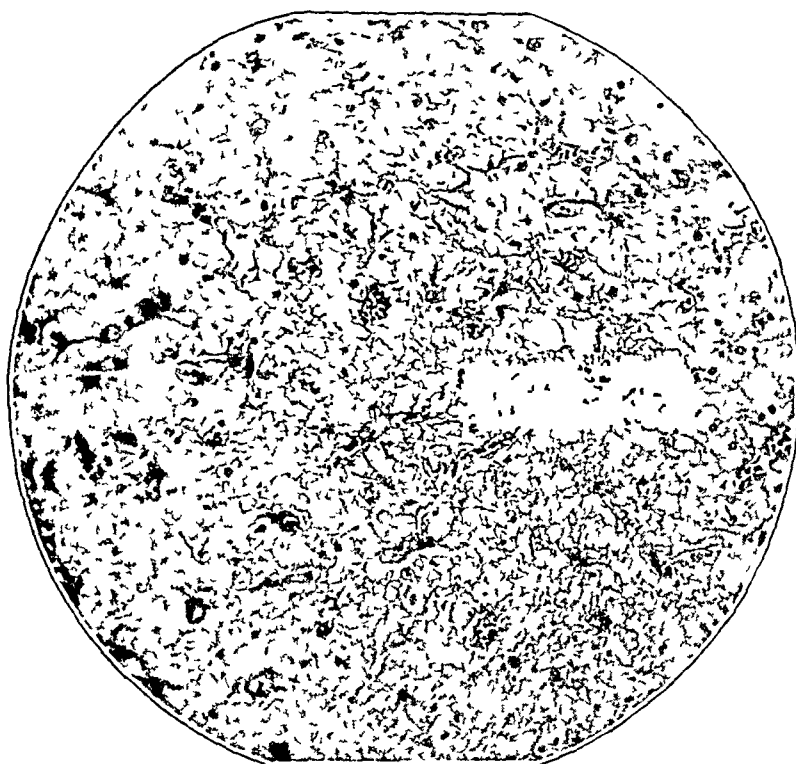


Fig 3—Higher magnification of the degeneration seen in figure 2. Note the spongy state of the tissue and the numerous astrocytes. Mallory's phosphotungstic acid-hematoxylin stain.

vessels constituted a striking feature of this lesion. This was well seen in sections stained with silver stain (fig 4), which demonstrated increase in perivascular connective tissue. Scattered through one such focus in the frontal lobe were several small petechial hemorrhages which had ruptured into the subarachnoid space. The arachnoid overlying this area was hyperplastic and infiltrated with red blood cells.

The ganglion cells appeared normal except in the foci of degeneration. Considerable gliosis of protoplasmic type was present throughout the cortex but was most marked in the temporal lobe. This gliosis was seen even in areas which had not undergone degeneration. A few small, spongy, demyelinated foci, bearing no relation to blood vessels, were encountered here and there in the white matter. In some areas the arachnoid was infiltrated to a slight degree with a small number of lymphocytes and plasma cells. Occasionally, the wall of a medium-sized vessel in the cortex was similarly infiltrated. The vessels, however, did not exhibit either thickening or thrombosis. The macroscopic cyst in the opercular region was surrounded by a zone of demyelination and gliosis.

Determination of arsenic was carried out on the fixed brain, and 0.005 mg as arsenous oxide ( $As_2O_3$ ) per hundred grams was found.

*Laboratory Data*—Repeated lumbar punctures yielded clear fluid under normal pressure. There was no abnormal cytologic response until April 19, the day after the patient lapsed into stupor, when examination of spinal fluid revealed 74 mononuclear cells per cubic millimeter. The Wassermann reaction of the blood and of the spinal fluid was 4 plus. Results of chemical examination of the blood and urinalysis were within normal limits. A blood count revealed mild leukocytosis.

*Autopsy*—General Examination. Gross examination. Significant changes were encountered in the lungs and the liver. Confluent areas of bronchopneumonia were scattered throughout the pulmonary fields. The liver weighed 1,000 Gm and exhibited a mild degree of fatty metamorphosis.

Histologic examination. Marked active congestion and many areas of acute bronchopneumonia were seen in the lung. The hepatic tissue was moderately swollen and congested. There were a few focal collections of round cells around the bile ducts and a slight increase in fibrous tissue in the periportal areas.

Examination of the Brain. Gross examination. Scattered small and discrete areas of bleeding into the subarachnoid space were revealed. The arachnoid was cloudy thickened and edematous over the superior convexities and at the base. The vessels of the pia exhibited

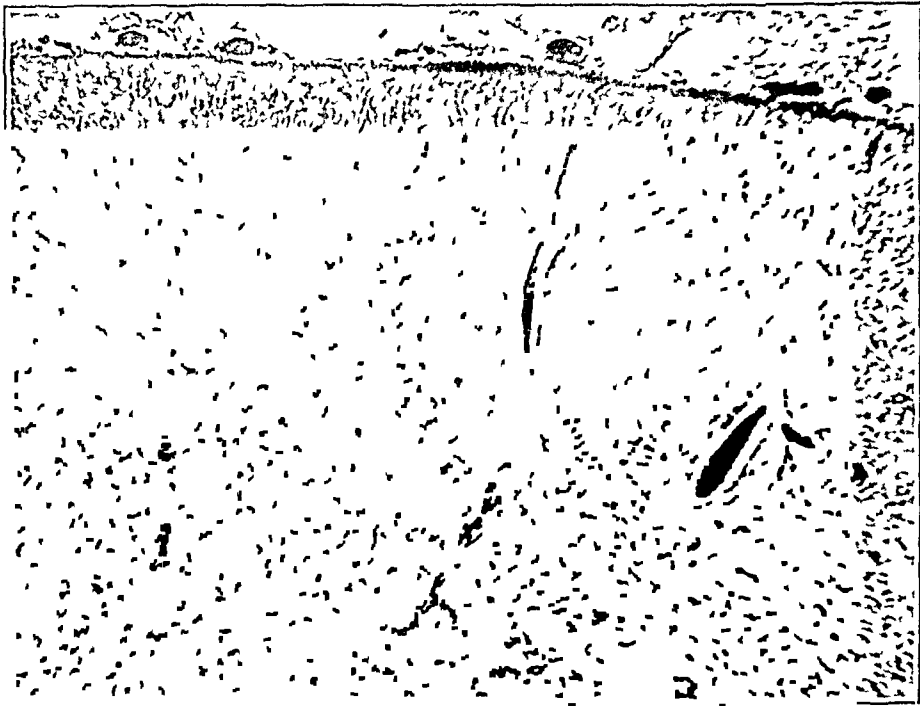


Fig 2—Diffuse degeneration seen in deeper layers of the cortex. Mallory's phosphotungstic acid-hematoxylin stain, medium magnification.

considerable congestion. The corpus callosum was poorly developed and was represented by only a thin strand of tissue half an inch (1.25 cm) in length in the region of the genu. The septum pellucidum was absent, and the columns of the fornix were rudimentary. The white matter was moderately congested. A small group of petechial hemorrhages, apparently related to the ventricular puncture, were seen in the white matter of the left parieto-occipital region. In the white matter of the left frontal operculum a small orange cyst was encountered. There was bilateral dilatation of the ventricular system, most marked in the right temporal horn.

Histologic examination. Sections from various parts of the brain were stained with hematoxylin and eosin, with Mallory's phosphotungstic acid-hematoxylin stain and by the methods of Spielmeyer, Mahan, Fincher and Cajal.

Edema was widespread but generally focal and most marked in the cerebral cortex. Considerable congestion and stasis were present in the small vessels and capillaries of the cortex, in the periventricular gray matter and, to a lesser extent, in the white matter. The stasis was often associated with the presence of a small number of red blood cells in the peri-

## COMMENT

Cerebral complications following the use of arsphenamine and related drugs are by no means rare. They have been described under various names, viz., hemorrhagic encephalitis, arsenical encephalitis, pericapillary encephalorrhagia, purpura of the brain, etc. Headache, vomiting, convulsions, unconsciousness, cyanosis and collapse, disturbances of the pupillary and extraocular muscles, loss of control of sphincters, mental disturbances and various types of paralysis are characteristic of the disorder. The symptoms are those of an acute diffuse cerebral disorder, and the clinical syndrome in this case conforms to that generally seen. In 104 cases of hemorrhagic encephalitis reviewed by Glaser, Imerman and Imerman<sup>7</sup> the symptoms of involvement of the central nervous system generally made their appearance in twelve hours to six days after an intravenous injection of an arsenical. A generalized convulsion marked the beginning of our patient's illness as is frequently the case and this occurred two hours after the injection of 0.04 Gm of mapharsen. The absence of changes in the spinal fluid in this case conforms to the experience of other authors.

There were, however, unusual clinical features in this case. Until now, in only 1 reported case have cerebral complications and fatal outcome been attributed to mapharsen. In Glaser's series any fatal cerebral complications always occurred before the fifteenth injection of an arsenical, 78 per cent of the complications occurring after one of the first three doses. Our patient had received forty-five injections of mapharsen. There was, however, an interval of six weeks between the forty-fourth and the forty-fifth injection. During that time a fracture of the femur had prevented the patient from attending clinic for treatment. In Glaser's analysis of 69 cases in which the survival period was stated, death occurred within eight days after the development of symptoms in all cases but 1. Our patient survived for twenty-one days.

The pathologic characteristics of arsphenamine encephalopathy have received considerable attention. The principal feature has been described as petechial hemorrhages, which often take a ring form. The hemorrhages generally were situated about small blood vessels and have been said to occur chiefly in the white matter. This hemorrhagic feature has been emphasized by most authors, but it is not the only form of pathologic change to be found. Earlier reports by Busse and Merian,<sup>8</sup> Schmorl<sup>9</sup> and Stuhmer<sup>10</sup> called attention to necrotic lesions in the brain in association with petechial hemorrhages or in their absence. Russell<sup>11</sup> reported 3 cases "in which administration of arsphenamine was followed by the production in the central nervous system not only of perivascular and ring hemorrhages, but also of perivascular non-hemorrhagic areas of necrosis and demyelination."

Roseman and Aring<sup>12</sup> have also reported a degenerative type of lesion in a case in which the complication developed after the fifteenth injection of neoarsphenamine. They stated "The most important lesions in the brain were focal perivascular areas of necrosis unrelated to hemorrhage in the white matter." The

7 Glaser, M. A., Imerman, C. P., and Imerman, S. W. So-Called Hemorrhagic Encephalitis and Myelitis Secondary to Intravenous Arsphenamines, *Am J M Sc* **189** 64, 1935.

8 Busse, O., and Merian, L. Ein Todesfall nach Neosalvarsaninfusion, *Munchen med Wchnschr* **59** 2330, 1912.

9 Schmorl, G. Encephalitis Hemorrhagica nach Salvarsaninjektionem, *Munchen med. Wchnschr* **60** 1685, 1913.

10 Stuhmer, A. Hirnschwellung nach Salvarsan, *Munchen med Wchnschr* **66** 96, 1919.

11 Russell, D. Changes in the Central Nervous System Following Arsphenamine Medication, *J Path & Bact* **45** 357, 1937.

12 Roseman, E., and Aring, C. D. Encephalopathy Following Neoarsphenamine Therapy, *New England J Med* **224** 550, 1941.



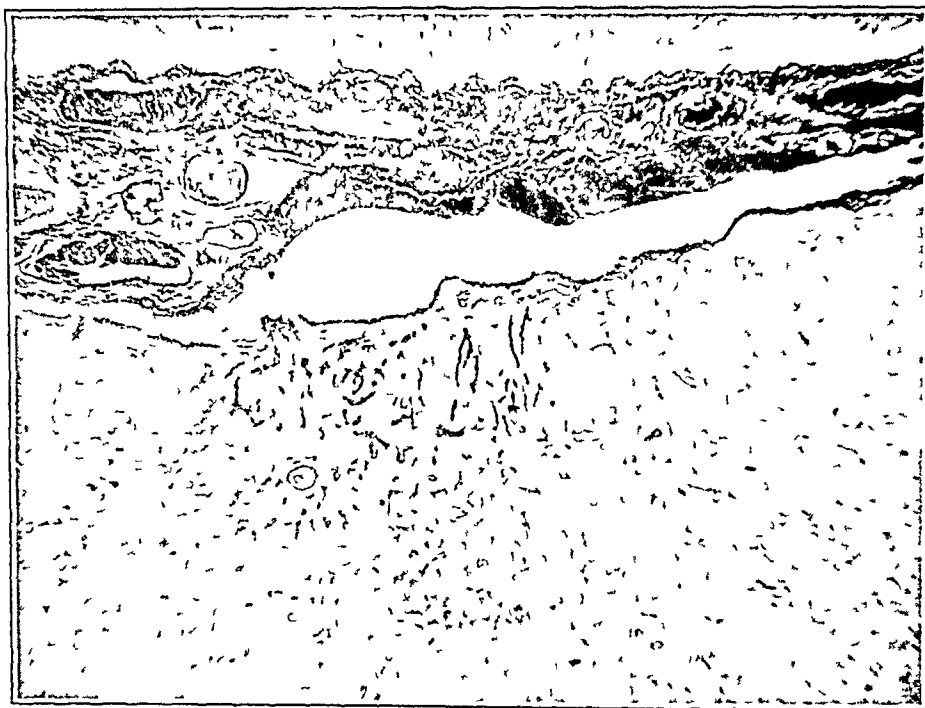


Fig 4—Discrete focal necrosis in the cortex. Note the vascular proliferation and the disappearance of cells in the lesion. Hemorrhagic exudate is evident in the subarachnoid space. Nissl's stain, low magnification.

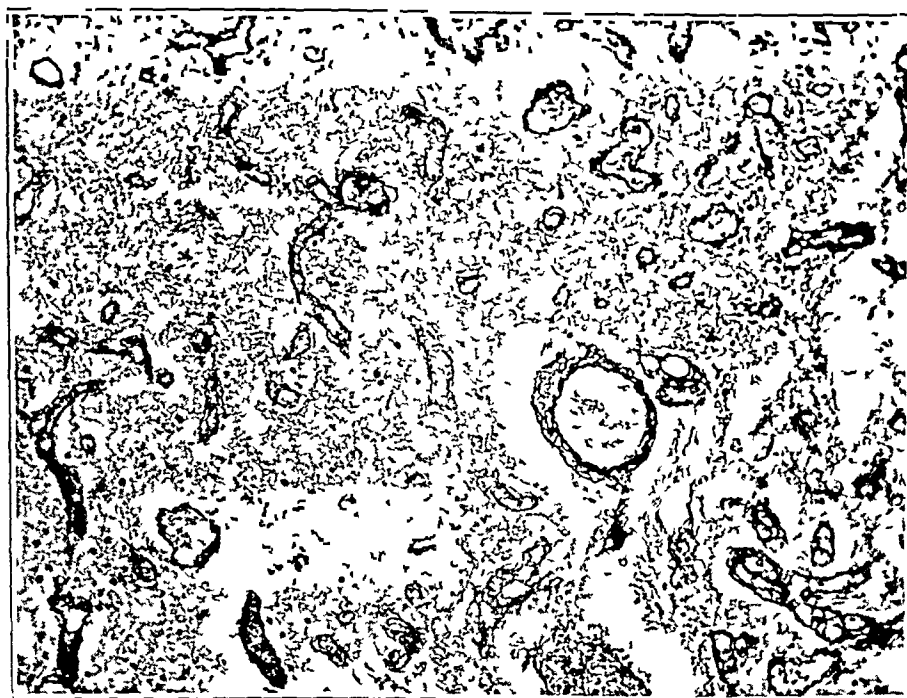


Fig 5—Higher magnification of the lesion seen in figure 4. Note the proliferation of the perivascular reticulum and the formation of new vessels. There is a spongy state of the tissue, and both ganglion cells and glia are absent. Fincher's stain, high magnification.

those in the brain have been rare. Pathologic studies have not as yet been reported. It is possible that these necrotic lesions may represent an unusual reaction of the brain to arsenic occurring under special circumstances and related to the time factor and the special conditions of tissue and vessel reactivity obtaining when prolonged administration of the drug is followed by a prolonged interruption in treatment, followed in turn by resumption of treatment.

As far as the hemorrhagic tendency is concerned, most of this was in relation to the ventricular puncture except for occasional small scattered petechial hemorrhages and the frequent small perivascular aggregates of phagocytes containing hemosiderin which indicated prior hemorrhage. Inasmuch as the patient had been well prior to the onset of the present illness, it is presumed that these represented hemorrhages which occurred early in the course of the illness and were therefore part of the response of the brain to arsenic. The necrotic-degenerative lesions and the gliosis were in excess of the hemorrhagic features and dominated the pathologic picture. This is more in keeping with the cases reported by Russell, by Roseman and Aving and by Pollak and Riehl.

In any event, petechial hemorrhages are not the only form of pathologic change encountered in the central nervous system as a complication of arsenical therapy. Indeed, hemorrhages may be in the background or even nonexistent. It would therefore be an error to ascribe the clinical picture to "hemorrhagic encephalitis" or "pericapillary encephalorrhagia." The broader term arsenical encephalopathy is considered more universally appropriate and does not commit one to the expectation of bleeding.

It should also be emphasized that when petechial bleeding occurs in the brain, the cerebrospinal fluid may give no indication of it. A clear spinal fluid should therefore not be considered to exclude the presence of petechial hemorrhages in the brain.

Although there was an increase in astrocytes in various regions of the cortex the ganglion cells were spared except in the necrotic foci and the areas of degeneration. The ganglion cells as such were therefore not affected primarily by the disease. In a few areas the meninges exhibited a small degree of localized infiltration by lymphocytes and plasma cells suggestive of syphilitic meningitis. A few vessels were similarly affected to a slight degree. But nowhere was there any thickening or sclerosis of vessels, thrombosis or occlusion to suggest that syphilis of the vascular system played any role in the genesis of the pathologic changes. In the absence of significant vascular disease the necrotic-degenerative lesions have been interpreted as toxic in origin. In the absence of previous neurologic illness the clinical syndrome was clearly related causally to the mapharsen. In its general features it conformed to the clinical features of reported cases of arsenical encephalopathy. The pathologic changes have therefore been ascribed to mapharsen.

#### SUMMARY

A case is presented in which fatal cerebral symptoms developed after mapharsen therapy.

The patient had received forty-five injections of the drug, but the last was preceded by an interval of six weeks during which the patient did not receive any medication.

The symptoms were those commonly seen in arsenical encephalopathy.

The pathologic changes in the brain consisted of petechial hemorrhages and necrotic-degenerative lesions of an unusual type.

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perivascular necrosis was related to changes in the small blood vessels, chiefly in the endothelium, which frequently occluded the vessel. Petechial hemorrhages did not seem to be important.

Pollak and Riehl<sup>13</sup> reported 2 cases of arsphenamine encephalopathy, in the first of which there was edema but no hemorrhages and microscopically revealed moderate degenerative changes in the ganglion cells and severe disease of the glia. They encountered increase in glia in the deepest layers of the cortex many of which were undergoing severe degeneration. One small area of necrosis was encountered in the pulvinar. The severe glial reaction in the cortex was similar to the marked cortical gliosis encountered in our case.

The pathologic alterations in the case reported here consisted of stasis, edema, petechial bleeding, degeneration and gliosis. An occasional ring hemorrhage was encountered. The fresh recent bleeding took place predominantly in the gray matter of the cortex, principally in the parieto-occipital region and seemed to be related to the ventricular puncture. Older more widespread perivascular petechial hemorrhages were represented by small necrotic, cribrate, perivascular foci containing small numbers of phagocytes loaded with hemosiderin. The macroscopic orange cyst in the white matter of the frontal operculum represented a hemorrhagic scar of this type. This cyst was surrounded by a zone of demyelination containing numbers of astrocytes. A similar lesion was described by Globus and Ginsburg.<sup>14</sup>

Lesions of a necrotic type, generally small and confined to the gray matter were a prominent part of the pathologic change in this case. One aspect of this necrotic-degenerative feature was characterized by small focal acellular areas in which there was proliferation of vessels and of perivascular connective tissue without gliosis. A second type of necrotic-degenerative lesion was more diffuse and confined to the cortex. The latter type is of special interest and calls for comment. This lesion extended for some distance in the gray matter of the cortex in a laminar fashion. The deeper layers were more severely involved, and the pathologic changes consisted of marked increase in astrocytes, a spongy state of the ground substance and total disappearance of the ganglion cells (see fig. 3). In the same region the more superficial layers demonstrated considerable increase in astrocytes, but the spongy state was lacking and the ganglion cells were less severely involved. Here the process seemed of the same type as that encountered deeper in the cortex, though less severe and less advanced. At times the severe phase extended throughout the thickness of the cortex. This type of lesion resembled the pathologic changes encountered by Pollak and Riehl. It seemed as though this process was progressive and continuous and had affected the deeper layers earlier and more severely. This conception of progressive degenerative changes occurring in the wake of a toxic process the acute phase of which had subsided was of a different order from the changes due to the toxin directly which could be considered as essentially hemorrhagic. This lends support to the view of Baker<sup>15</sup> and Russell<sup>11</sup> that the degenerative features belonged to processes of longer duration and were related to the time factor. The necrotic foci encountered in our case, however, are unlike those described by Russell, inasmuch as hers were simply demyelinating lesions.

The significance of these lesions is not clear. Whether they represent a mapharsen effect is not known. Reactions to mapharsen have been too few, and

13 Pollak, E, and Riehl, G, Jr. Zur Pathologie der Salvarsanschaden des Nervensystems, *Jahrb f Psychiat u Neurol* **47** 99, 1930.

14 Globus, J. H., and Ginsburg, S. W. Pericapillary Encephalorrhagia Due to Arsphenamine. So-Called Arsphenamine Encephalitis, *Arch Neurol & Psychiat* **30** 1226 (Dec.) 1933.

15 Baker, A. B. Hemorrhagic Encephalitis. *Am J Path* **11** 185 1935.

consultant saw no indication for surgical intervention since the tonsil and the pharynx were normal in appearance. The tenderness and swelling of the right side of the neck and the slight protrusion of the right tonsil disappeared after three days. The fever and chills continued. The hemoglobin determination dropped to 56 per cent and the erythrocyte count to 2,430,000. The leukocytes ranged from 7,600 to 13,000 per cubic millimeter, the neutrophils varied from 75 to 90 per cent. Five blood cultures were sterile. Agglutination tests for tularemia, typhoid, paratyphoid and undulant fever were negative. The Wassermann and Kahn tests of the blood were negative. The urine was essentially normal. Sulfanilamide was administered to the patient shortly after her admission to the hospital. She received a total of 1,290 grains (83.4 Gm) in twenty-three days. The drug had no effect on her condition. The only other treatment consisted of nine blood transfusions, averaging 250 cc, and general supportive measures. The oral temperature continued to swing from 99 to 106 F daily. There were no subjective symptoms other than weakness, anorexia, chills and sweating. General physical examination disclosed only a soft systolic blow at the mitral area. The development of a cardiac murmur suggested the possibility of acute bacterial endocarditis, but the negative blood cultures and the absence of embolic phenomena precluded this diagnosis.

On May 15 slight swelling reappeared at the angle of the right jaw. This was slightly tender and similar to that noted on May 4. Because of these signs and because of the persistence of sepsis, a diagnosis of jugular phlebitis was made despite the negative blood cultures and the normal appearance of the tonsil and the pharynx.

On May 16 Dr S. Rosenberg exposed the internal jugular vein on the right side. Moderate difficulty was encountered in exposing the carotid sheath, as the latter was infiltrated and adherent to several enlarged, inflamed lymph nodes. The internal jugular vein was discolored and presented a dull white appearance in contrast to the usual blue color. The vein had lost its elasticity and was unaffected by the respiratory excursions. A ligature was placed about the vein in the lower part of the neck, and a small portion was excised. There was no mural thrombus at the site of ligation, but the wall of the vein was definitely thickened. The right tonsil was removed by Dr S. Ratner. When the tonsil was raised from its bed, about 2 ounces (59 cc) of pus gushed from the space behind it. In the lateral pharyngeal wall at the level of the tonsil was a large perforation through which pus oozed. It communicated with an abscess cavity which occupied the parapharyngeal space.

The postoperative course was stormy. The oral temperature ranged from 96 to 106 F for five days. On the sixth day the temperature became normal. During the next two weeks there was no further rise in temperature or recurrence of chills. The cardiac murmur disappeared. After a stay of thirty-eight days in the hospital the patient was discharged completely recovered. At the time of writing she has remained well for four years.

The pus obtained from the abscess yielded a growth of staphylococci on culture. The pathologic findings were (1) retrotonsillar abscess, (2) perforation of the constrictor pharyngeus superior muscle, (3) parapharyngeal abscess, (4) acute cervical lymphadenitis and (5) phlebitis of the internal jugular vein.

*Summary*—A septic temperature (96 to 106 F), chills and sweats appeared in a patient immediately after a mild sore throat and persisted for twenty-six days. Transient slight swelling and tenderness at the angle of the jaw were the only signs of infection present. Operation revealed a retrotonsillar abscess with extension of the infection to the parapharyngeal space and phlebitis of the internal jugular vein. The patient was cured by tonsillectomy and ligation of the internal jugular vein.

**CASE 2**—H. H., a white man aged 51, previously in good health, became ill on Feb 17, 1941 with malaise, muscular aches, chilliness, sweating and slight soreness of the left side of the throat. The oral temperature was 102 F, the pulse rate was 110 and the respiratory rate 18 per minute. Physical examination disclosed only moderate congestion of the pharynx and slight swelling and redness of the left tonsil. The sore throat lasted two days. On the fourth day the patient began to have pain and slight swelling of the right knee, the left elbow and the metacarpal joints of the right middle finger. The involvement of these joints subsided within a week, but the fever persisted. The oral temperature ranged from 98 to 102 F daily, the pulse rate was 70 to 110 per minute. There were no subjective symptoms other than anorexia, weakness, night sweats and loss of 15 pounds (6.8 Kg) during the following month.

On March 18 slight soreness of the left side of the throat recurred and lasted two days. The pharynx was congested, but the tonsils showed no evidence of infection. The general physical examination gave completely negative results except for the development of a soft systolic murmur over the mitral area during the fifth week of illness. Repeated urinalysis failed to reveal any abnormalities. The white cells ranged from 11,000 to 13,000 per cubic millimeter of blood, with 80 to 85 per cent polymorphonuclears present.

# POSTANGINAL SEPSIS

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Septicemia may be due to a number of causes. It is important to determine the exact cause in order that proper treatment may be instituted. The purpose of this paper is to call attention to one cause of septicemia often overlooked by the physician, namely, septic phlebitis of the internal jugular vein or of one of its branches<sup>1</sup>. This condition is usually called postanginal sepsis or postanginal pyemia<sup>2</sup> because it almost always follows an infection of the throat. Failure to recognize this dangerous disease has resulted in many fatalities. Early diagnosis and operation may save the life of the patient.

Few reports of cases of postanginal sepsis are found in the American literature, although German and French observers have published many. Two cases are reported here to illustrate the clinical picture and the diagnosis of this entity.

## REPORT OF CASES

CASE 1—D W, a white girl of 15, was admitted to the Montefiore Hospital April 21, 1938. The past medical history was without import. The illness began on April 17 with stuffiness of the nose and slight soreness of the right side of the throat, the latter lasting about two hours. On the second day the oral temperature was 101 F, the pulse rate 95 and the respiratory rate 18 per minute. Physical examination disclosed only slight prominence and redness of the right tonsil. There was no enlargement of the cervical gland. The ears, the pharynx, the nose and the paranasal sinuses were normal. On the third and fourth day of the illness the patient had fever, slight chilliness and sweating but no sore throat.

On April 21 the oral temperature was 105 F, the pulse rate 130 and the respiratory rate 22 per minute. A slight cough had developed during the past few hours. Physical examination gave completely negative results, the slight redness and prominence of the right tonsil were now absent. The patient was admitted to the hospital with a diagnosis of central pneumonia. Roentgen examination, however, revealed normal lungs. A specimen of urine obtained by catheter revealed no abnormalities. The hemoglobin determination was 75 per cent, the red cells numbered 3,640,000 and the white cells numbered 18,400 per cubic millimeter of blood, with 86 per cent polymorphonuclear cells present.

From April 22 to May 3 the patient was critically ill. For days the oral temperature ranged from 96 to 99 F in the morning and from 105 to 106.7 F in the afternoon or evening. On other days the temperature was continuously elevated, 103 to 105 F. The pulse rate varied from 90 to 140 per minute. The patient had frequent severe chills, followed by profuse sweating. The physical examination, including pelvic and neurologic examinations, gave entirely negative results during the first twelve days of hospitalization. The clinical impression was sepsis of unknown origin.

On May 4 examination revealed a new condition, namely, slight swelling of the right side of the neck at the level of the angle of the jaw. This was slightly tender and seemed to lie beneath the sternocleidomastoid muscle. At the same time slight prominence of the right tonsil reappeared, similar to the finding of April 18. The occurrence of these slight abnormalities on the same side as the recent soreness of the throat suggested the possibility of a deep infection of the neck associated with phlebitis of the internal jugular vein to explain the clinical picture of sepsis. Operation on the right side of the neck was advised, but a surgical

1 Mosher, H P. Submaxillary Fossa Approach to Deep Pus in the Neck, *Tr Am Acad Ophth* **34** 19, 1929.

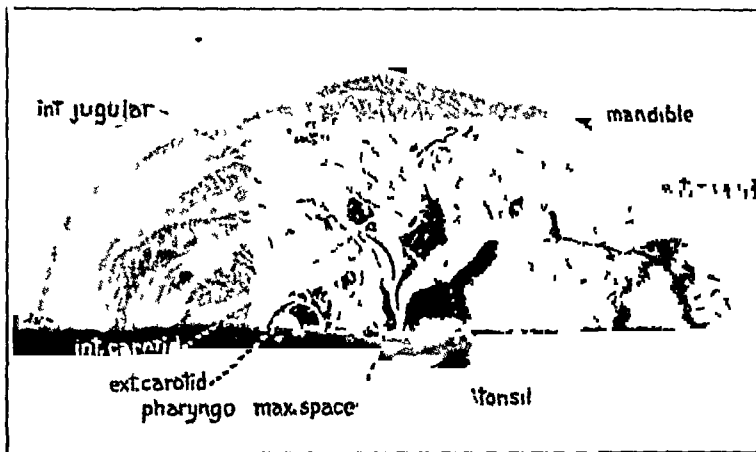
2 (a) Abt, I A. Postanginal Sepsis, *J Pediat* **1** 8 (July) 1932. (b) Waldapfel, R. Die postanginose Pyämie, *Ztschr f Hals-, Nasen- u Ohrenh* **23** 178, 1929. (c) Burchardt, S. Ein Beitrag zur Pathogenese der postanginösen Sepsis, *ibid* **23** 97, 1929.

## BACTERIOLOGY

The organism most frequently associated with postanginal sepsis is an anaerobic streptococcus *Streptococcus viridans* and *Staphylococcus aureus*, *Pneumococcus*, *Staphylococcus albus*, *Staphylococcus aureus* and an anaerobic bacillus have also been found in this lesion<sup>3</sup>

## ANATOMY

In order to understand the pathologic nature of this disease with its resultant clinical picture, an appreciation of the anatomy of the parapharyngeal space is important. This has been discussed fully by Mosher<sup>4</sup> and others<sup>5</sup>. In the accompanying photograph are shown the essential features of the parapharyngeal space. The latter is a connective tissue space that lies lateral to the pharynx and extends from the base of the skull to the angle of the jaw, a distance of 2.5 cm. It is separated medially from the tonsil by the superior constrictor pharyngeus muscle. The lateral border is formed by the internal pterygoid muscle, the ascending ramus of the jaw and the capsule of the parotid gland. The upper cervical vertebrae covered by the prevertebral muscles form the posterior boundary. The parapharyngeal space contains the ninth to twelfth cranial nerves, a few lymphatic glands, the



Horizontal section of the head at the level of the tonsil (after Hall<sup>5a</sup>)

internal carotid artery and the internal jugular vein. It communicates with the cranium through the carotid canal and the jugular foramen and with the mediastinum by the carotid sheath.

## PATHOGENESIS AND PATHOLOGY

The source of this disease is usually an infection in or about the tonsils<sup>1</sup>. The disease may occur during or after an acute abscess of the throat,<sup>6</sup> such as an intratonsillar, a peritonsillar, a retrotonsillar or a retropharyngeal abscess, or it

3 (a) Beck, A. L. Deep Neck Infection, *Ann Otol, Rhin & Laryng* **48** 940 (Dec.) 1939. (b) Hirsch, C. Septicemia Following Tonsillitis, *New York State J. Med* **35** 767 (Aug. 1) 1935. (c) Reye, E. Zur Pyämie nach Angina, *Med. Welt* **4** 1791 (Dec. 13) 1930.

4 Mosher, H. P. Deep Cervical Abscess and Thrombosis of the Internal Jugular Vein. *Laryngoscope* **30** 365 (June) 1920.

5 (a) Hall, C. The Parapharyngeal Space, *Ann Otol, Rhin & Laryng* **43** 793 (Sept.) 1934. (b) Shapiro, S. L. Deep Cervical Infection Following Tonsillectomy, *Arch. Otolaryng.* **11** 201 (June) 1930.

6 (a) Deering, W., and Brennemann, J. Acute Abscess of the Throat, *J. A. M. A.* **118** 1171 (April 4) 1942. (b) Beck, A. L. A Study of Twenty-Four Cases of Neck Infection, *Tr. Am. Acad. Ophth.* **37** 342, 1932. (c) Haymann, L. Erhebungen über die tonsillo-gene Sepsis, *Ztschr. f. Hals-, Nasen- u. Ohrenh.* **35** 288, 1934.

On March 28 the patient was awakened from sleep by severe pain in the left side of the chest and difficulty in breathing. The pain lasted several hours and was increased by deep inspiration. The temperature rose to 103 F. Physical examination revealed a pleural rub, diminished breath sounds and impaired resonance at the base of the left lung. The signs of disease in the chest lasted four days and were associated with slight cough, but there was no hemoptysis. The temperature and sweating gradually subsided, and the condition of the patient slowly improved during the following week.

Between April 4 and April 11 there was no sweating or elevation of temperature. The slight systolic murmur at the mitral area persisted. The clinical diagnosis was acute rheumatic fever associated with mitral endocarditis and pleurisy.

On April 12 fever and sweating returned. The oral temperature ranged from 99 to 103 F daily, and the pulse rate varied from 90 to 120 per minute. The patient received 60 to 90 grains (3.88 to 5.82 Gm) of sodium salicylate daily. The medication had no effect on the patient's condition.

On April 24 a severe chill developed, followed by marked sweating. The oral temperature rose to 105 F, and the pulse rate was 140 per minute. Marked prostration was present. The clinical diagnosis of acute rheumatic fever seemed untenable. The possibility of subacute bacterial endocarditis was considered on account of the systolic mitral murmur, but there was no evidence of embolic phenomena or of enlargement of the spleen.

The patient was admitted to the hospital on April 28. The hemoglobin determination was 87 per cent, the red cells numbered 4,100,000 and the white cells from 9,700 to 14,600 per cubic millimeter of blood, with 75 to 80 per cent polymorphonuclears present. The urine was normal except for occasional red and white blood cells. Two blood cultures showed no growth. Agglutination tests for typhoid, paratyphoid, tularemia and undulant fever were negative. The Wassermann and Kahn tests of the blood were also negative. There was no evidence of malaria in the blood smears. Cutaneous tests with tuberculin were negative. A roentgenogram of the chest taken on April 30 revealed normal lungs and a normal heart. The patient received 60 grains of sulfathiazole (2-[paraaminobenzenesulfonamido]-thiazole) daily without any benefit.

Because a satisfactory explanation for the persistent fever was lacking, and because the fever had followed a mild but definite sore throat, the possibility of postanginal sepsis was first suspected on May 1, ten weeks after the onset of the illness. Examination of the neck revealed a localized area of tenderness at the angle of the left jaw but no swelling or induration. This finding had previously escaped recognition, probably because postanginal sepsis had not been considered and the neck had not been carefully examined.

On May 4 pain suddenly developed in the left lower region of the chest, with difficulty in breathing, followed by slight cough and slight hemoptysis. Physical examination revealed impaired resonance and diminished breath sounds over the lower lobe of the left lung. Roentgen examination revealed an elevation of the left side of the diaphragm and a triangular shadow in the lower lobe of the left lung typical of pulmonary infarction. It was felt that the entire clinical picture could be explained on a single basis, i. e., an infection in or around the tonsil, complicated by phlebitis of one of the veins of the neck and infarction of the lung. The patient was seen in consultation by Dr. Alexander Colwell, who advised tonsillectomy.

Tonsillectomy was performed on May 5 by Dr. J. McCready. As the left tonsil was removed, a large amount of pus welled up from the crypts. There was no pus behind the tonsil, and the superior constrictor pharyngeus muscle was intact. By cutting across the left tonsil an abscess cavity was found, measuring 8 by 8 mm, filled with pus. Microscopically, the wall of the abscess consisted of a slight amount of fibrous tissue infiltrated by polymorphonuclear and lymphocytic cells. The pus obtained from the abscess yielded growths of *Streptococcus haemolyticus* and *Staphylococcus aureus* on culture, but there was no evidence of the tubercle bacillus. The right tonsil showed no gross or microscopic evidence of infection.

The temperature ranged from 99 to 102 F for four days after the operation. On the fifth day it returned to normal. The signs and symptoms of involvement of the chest slowly cleared up, and the patient's general condition improved during the following week. There was no further rise in temperature or recurrence of sweats. The cardiac murmur disappeared. The patient was discharged from the hospital on May 14 completely recovered. At the time of writing he has remained well for fourteen months.

*Summary*—A patient had night sweats and an intermittent fever (99 to 103 F) for twelve weeks following mild pharyngitis and tonsillitis. Because of painful joints and a systolic mitral murmur, the condition was first incorrectly diagnosed as acute rheumatic fever. The patient had two bouts of pulmonary infarction during the fifth and twelfth weeks of his illness. Tenderness of the angle of the jaw was the only sign of infection. Operation revealed a small intratonsillar abscess. Recovery followed tonsillectomy, without ligation of the internal jugular vein.

## CLINICAL FEATURES

The onset of the disease is often insidious, beginning with a mild infection of the upper respiratory tract <sup>21</sup> The sore throat may be slight and fleeting, as in the reported cases, and easily overlooked On the other hand, the disease may be ushered in with severe symptoms when a marked infection is present in the throat

The symptoms of this condition may be divided into two categories (1) local and (2) systemic

The local symptoms—pain, trismus, torticollis, dysphagia or hoarseness—are due to the primary infection of the throat, to the parapharyngeal abscess or to both Although local symptoms are usually present, it is important to remember that they may be transient or completely absent, as in the patients described in a foregoing section of this paper <sup>7b</sup> The absence of local symptoms is deceptive and often responsible for diagnostic errors

The systemic symptoms are due principally to suppurative phlebitis of the internal jugular vein or of one of its tributaries The symptoms vary, depending on the virulence of the infecting organisms They may occur during or immediately after the infection of the throat, or they may be delayed as long as sixty days after the primary infection has healed <sup>6b</sup> The average patient has a latent or asymptomatic period of fourteen days between the infection of the throat and the appearance of sepsis

The systemic symptoms are those of any septicemia high fever, chilliness or chills, sweating, rapid pulse, rapid respiration and prostration, with or without delirium A review of the cases reported in the literature reveals two types of temperature curves (1) The fever may be of the septic type and associated with chills, (2) a continuous high temperature may be present without chills In unusual instances, <sup>3c</sup> as in case 2, a low grade or moderate fever, with or without remissions, may be present a number of weeks before high fever and chills develop It is important to note that chills or positive blood cultures have appeared in only 50 per cent of the reported cases <sup>22</sup> Their absence, therefore, is of no diagnostic importance Jaundice <sup>18b</sup> is not unusual and is probably due to damage of the liver or to hemolysis of red blood cells The spleen may be enlarged and palpable Lesions of the skin, such as petechiae or purpura, may be present <sup>6a</sup> Pain <sup>18b</sup> may occur in the joints, as in case 2, and simulate acute rheumatic fever Secondary anemia usually develops The leukocyte count has varied from 5,000 to 60,000 in the reported cases, and usually there has been an increase in the polymorphonuclear cells Albuminuria is common Hematuria <sup>23</sup> may occur as a result of infarction of the kidney or of complicating nephritis <sup>18b</sup>

There may be symptoms referable to the hypoglossal, glossopharyngeal, vagus or accessory nerves as a result of extension of the infection to these nerves as they pass through the parapharyngeal space <sup>3b</sup>

Sooner or later grave complications occur Fatal hemorrhage has been reported in parapharyngeal infection, due to erosion of the internal or the external carotid artery <sup>24</sup> The infection may extend down the carotid sheath to the mediastinum to produce severe dyspnea or asphyxia <sup>3a</sup> The most frequent complications are pulmonary, infarction, abscess, pneumonia or empyema <sup>25</sup> Metastatic abscesses of the

21 Hirsch <sup>3b</sup> Beck <sup>6b</sup> Hall <sup>7b</sup>

22 Hirsch <sup>4b</sup> Beck <sup>9a</sup>

23 Matis, E I Two Unusual Cases of Postanginal Sepsis, *Ann Otol, Rhin & Laryng* 49 559 (June) 1940

24 Salinger, S, and Pearlman, S J Hemorrhage from Pharyngeal and Peritonsillar Abscess, *Arch Otolaryng* 18 464 (Oct) 1933

25 Kissling <sup>7a</sup> Dixon and Helwig <sup>11a</sup> Knick <sup>14</sup>



may follow mild tonsillitis or pharyngitis<sup>7</sup> In a small percentage of the cases it follows tonsillectomy<sup>8</sup> and infections of the ear, adenoids, the floor of the mouth, a jaw, a cervical vertebra, a parotid gland, the nose, the paranasal sinuses or the mastoid<sup>9</sup>

In most cases of postanginal sepsis, as in case 1, the infection extends from the throat through a constrictor pharyngeus muscle to produce cellulitis or an abscess in the parapharyngeal space<sup>10</sup> Phlebitis of the internal jugular vein is apt to occur as a result of invasion of the wall of the vein by the infection present in the parapharyngeal space<sup>11</sup> In a small percentage of reported cases, as apparently in case 2, there is no pus in the parapharyngeal space, the lesion is primarily phlebitis of the small veins of the tonsil, which may extend through the facial vein to involve the internal jugular vein<sup>12</sup> Whether the lesion involves the internal jugular vein together with its tributaries, or whether the phlebitis is limited to the tonsillar,<sup>13</sup> the facial<sup>14</sup> or the internal jugular vein,<sup>15</sup> the end result is the same The organisms directly invade the blood stream

A review of 105 reported cases reveals that the degree of phlebitis noted at operation or at autopsy varies from slight microscopic changes in the wall of a patent vein<sup>16</sup> to the characteristic whitened and thickened vein containing an adherent purulent thrombus<sup>17</sup> In some instances, as in case 1, a whitened, thickened vein containing fluid blood or fluid pus may be observed or there may be suppurative periphlebitis<sup>18</sup>

An analysis of clinical and postmortem observations indicates that there is no definite correlation between the degree or extent of phlebitis and the severity of the symptoms Severe septicemia may occur with slight or marked phlebitis, with or without thrombosis<sup>19</sup> Thrombosis is important, however, since infected thrombi are frequently responsible for septic infarcts of the lung<sup>20</sup> From these infarcts, or as a result of the direct passage of bacteria through the pulmonary capillaries, metastatic abscesses may occur in other parts of the body

7 (a) Kissling, K Ueber postanginöse Sepsis, *München med Wchnschr* **76** 1163 (July 12) 1929 (b) Hall, C Sepsis Following Pharyngeal Infections, *Ann Otol, Rhin & Laryng* **48** 905 (Dec) 1939 Hirsch<sup>3b</sup>

8 (a) Reuben, M S Postanginal Sepsis, *Arch Pediat* **52** 152 (March) 1935 (b) Shapiro<sup>5b</sup>

9 (a) Beck, A L Parapharyngeal Infections and Internal Jugular Vein Thrombosis Diagnosis and Treatment, *Laryngoscope* **44** 431 (June) 1934 (b) Reuben<sup>8a</sup>

10 (a) Waldapfel, R Post-Tonsillitis Pyemia, *Tr Am Acad Ophth* **33** 291, 1928 (b) Hirsch<sup>3b</sup>

11 (a) Dixon, O J, and Helwig, F C Thrombophlebitis of the Internal Jugular Vein as a Complication of Tonsillitis, *Ann Otol, Rhin & Laryng* **39** 1137 (Dec) 1930 (b) Joel, W Ueber die postanginöse Pyämie und ihre Verbreitungswege, *Deutsche med Wchnschr* **55** 2133 (Dec 20) 1929 Hirsch<sup>3b</sup> Mosher<sup>4</sup> Hall<sup>7b</sup>

12 Fraenkel, E Pyämie nach Angina, *Deutsche med Wchnschr* **52** 93 (Jan 15) 1926 Waldapfel<sup>10a</sup>

13 Hall<sup>7b</sup> Beck<sup>9a</sup> Waldapfel<sup>10a</sup>

14 Knick Die operative Heilung der tonsillären Sepsis, *Ztschr f Hals-, Nasen- u Ohrenh* **18** 546, 1927-1928

15 Waldapfel<sup>10a</sup> Dixon and Helwig<sup>11a</sup>

16 Burchardt<sup>2c</sup> Beck<sup>6b</sup> Knick<sup>14</sup>

17 Hirsch<sup>3b</sup> Mosher<sup>4</sup> Dixon and Helwig<sup>11a</sup>

18 (a) Bertelsmann, R Ueber Postanginöse Sepsis sive Bakteriämie, *Zentralbl f Chir* **54** 642 (March 12) 1927 (b) Rubin, H Pyemia Following Acute Tonsillar Infections, *Arch Otolaryng* **17** 183 (Feb) 1933 Kissling<sup>7a</sup>

19 Bertelsmann, R Postanginöse Sepsis und die Lymphbahnen, *Zentralbl f Chir* **54** 1949 (July 30) 1927 Beck<sup>6b</sup> Hall<sup>7b</sup>

20 Kissling<sup>7a</sup> Dixon and Helwig<sup>11a</sup>

anterior border of the sternocleidomastoid muscle. Occasionally, there may be some swelling of the parotid gland with infection of the parapharyngeal space<sup>33</sup>. These signs, however, are frequently absent in patients with phlebitis or thrombosis of the internal jugular vein,<sup>34</sup> so that they cannot be relied on constantly in diagnosis. Tenderness at the angle of the jaw on the involved side, with or without slight swelling, may be the only presenting sign<sup>35</sup>. This sign is present in most if not all cases,<sup>29</sup> but it may be transient, as in case 1. Unless the disease is kept in mind and the neck and the throat carefully and repeatedly examined, the source of the sepsis may not be discovered. Minor evidence of infection should suffice for the diagnosis particularly when all other causes of septicemia have been ruled out. To wait for the development of marked edema or tenderness in the presence of relatively slight but definite signs may prove fatal<sup>36</sup>. To wait for a positive blood culture may also be fatal, since in this condition cultures are frequently found negative<sup>36</sup>.

#### DIFFERENTIAL DIAGNOSIS

A review of the literature reveals the fact that many patients with this condition have died with the clinical diagnosis of "septicemia of unknown origin"<sup>1</sup> or with a diagnosis suggesting that the disease has been confused with a number of other diseases. The more important of these are pneumonia, thrombosis of a lateral sinus, acute or subacute bacterial endocarditis, acute renal infection, blood dyscrasia, acute osteomyelitis and meningitis.

*Pneumonia*—Metastatic lesions of the lungs (infarction or abscess) are common in postanginal sepsis and have often been confused with pneumonia<sup>7b</sup>. In differentiating these conditions, the history and the sequence of events are important. The history of attacks of "pleurisy" or "pneumonia" during or after an infection of the throat, as in case 2, should suggest the possibility of phlebitis of a vein of the neck with pulmonary metastasis. A careful search must be made of the neck and the throat for evidence of this condition. Septicemia or pyemia may occur in pneumonia, but there is usually clearcut evidence of a severe pulmonary infection from the start. The reverse holds true for postanginal sepsis, in which signs and symptoms of septicemia precede involvement of the lungs.

*Thrombosis of a Lateral Sinus*—Postanginal sepsis may be mistaken for thrombosis of a lateral sinus when suppuration of the middle ear complicates an acute infection of the throat<sup>18b</sup>. Signs and symptoms of sepsis, a positive blood culture and changes in the eyegrounds are common to both conditions. Clinical or roentgen evidence of acute mastoiditis is indicative of thrombosis of a lateral sinus. In the absence of mastoiditis pain, swelling or tenderness of the neck or the throat is highly suggestive of postanginal sepsis. When the infection of the middle ear and throat occur on the same side, a positive Tobey-Ayer test is of no value in differential diagnosis, since an occluding thrombus of the internal jugular vein may occur in either condition. With otitis on the side opposite the infection of the throat, a positive Tobey-Ayer test may be of localizing or diagnostic value<sup>18b</sup>. A negative test is, however, of no diagnostic importance since the test is negative with simple phlebitis, with a mural thrombus of the internal jugular vein or with thrombophlebitis of the tonsillar or the facial vein.

*Acute or Subacute Bacterial Endocarditis*—The local evidence of postanginal sepsis may be slight and overshadowed by septicemia. Soft mitral systolic murmurs

33 Abt<sup>2a</sup> Beck<sup>3a</sup>

34 Beck<sup>6b</sup> Stahl<sup>27a</sup>

35 Hall<sup>7b</sup> Claus<sup>29</sup>

36 Hirsch<sup>3b</sup> Hall<sup>7b</sup> Beck<sup>9a</sup> Claus<sup>26b</sup>

bones, the joints, the muscles, the brain, the liver and the kidneys are common. Meningitis or infection of a cavernous sinus with ocular symptoms has occurred in 10 per cent of the fatal cases. Such developments are due to retrograde extension of the phlebitis and involvement of the jugular bulb and the sigmoid sinus or of the pterygoid plexus and the ophthalmic vein in this condition.<sup>26</sup> These complications may obscure and prevent diagnosis of the primary disease.

The disease pursues a highly variable course. It may continue for periods between a few days and several months, depending on the severity of the sepsis and the presence or the absence of complications.<sup>27</sup> Death occurs in almost 100 per cent of the cases if the condition is unrecognized and untreated.<sup>28b</sup>

#### DIAGNOSIS

As with other diseases, postanginal sepsis is often overlooked either because the physician is unfamiliar with its varying manifestations or because he fails to consider such a diagnosis. It has been estimated that of every 100 cases in which death occurred from this disease, in only 20 was the condition recognized during life.<sup>28</sup>

The development of septicemia or pyemia during or after an infection of the throat should suggest the possibility of suppurative inflammation of the veins of the neck. As a rule, the presence of an infection of the throat is evident from the history and the physical signs, but occasionally there may be no clue to the source of the sepsis. The initial infection may be slight and fleeting,<sup>29</sup> or it may be present weeks before the onset of sepsis,<sup>30</sup> and thus it may be completely overlooked. In addition, there may be no local signs or symptoms to direct attention to the throat when the patient comes under observation with a septic temperature, chills or metastatic symptoms.<sup>29</sup> The condition usually passes under the guise of septicemia of unknown origin<sup>1</sup>; the primary disease is overlooked during life and first recognized at postmortem examination.

Provided the possibility of postanginal sepsis is considered, the diagnosis may be made for every patient presenting the clinical picture of septicemia or pyemia of unknown origin. Sepsis from other causes, such as diseases of bone or of the ear or acute bacterial endocarditis, must of course be excluded. In the absence of any demonstrable cause of sepsis, a history of recent inflammation of the throat, however slight, must always lead to the suspicion of phlebitis of the internal jugular vein or of one of its branches. Slight swelling of the lateral wall of the pharynx or displacement or swelling of the tonsil may be additional evidence of this disease,<sup>30</sup> but the absence of these signs is of no diagnostic value.<sup>30</sup> In the presence of a normal throat the diagnosis must rest on the history of an infection of the throat plus a careful examination of the neck of the patient. The involved vein is rarely palpable,<sup>29</sup> but swelling,<sup>18b</sup> tenderness<sup>31</sup> or induration<sup>32</sup> may occur along the

26 (a) Long, J. W. Excision of Internal Jugular Vein for Streptococcic Thrombi Vein and Cavernous Sinus Causing Paralysis of Orbital Muscles, *Surg., Gynec. & Obst.* **14** 86 1912. (b) Claus, H. Acht und zwanzig Falle von Pyämie nach Angina, *Ztschr. f. Hals-Nasen- u. Ohrenh.* **21** 114, 1929. (c) Hirsch.<sup>3b</sup> (d) Rubin.<sup>18b</sup>

27 (a) Stahl, R. Zur Kenntnis der Thrombophlebitis und Sepsis postanginosa. *Deutsche med. Wchnschr.* **53** 186 (Jan 28) 1927. (b) Fiaenkel.<sup>12</sup>

28 Mlechlin, B., cited by Matis.<sup>28</sup>

29 Claus, H. Bemerkungen zur Pyämie nach Angina, *Ztschr. f. Hals- Nasen- u. Ohrenh.* **18** 557, 1927. Hall.<sup>7b</sup> Claus.<sup>26b</sup>

30 Hall.<sup>7b</sup> Claus.<sup>26b</sup> Claus.<sup>29</sup>

31 Hall.<sup>7b</sup> Beck.<sup>9a</sup> Rubin.<sup>18b</sup> Matis.<sup>23</sup>

32 Goodman, C. Primary Jugular Thrombosis Due to Tonsil Infection, *Ann. Otol. Rhin. & Laryng.* **26** 527, 1917.

pletely overlooked. A history of recent soreness of the throat, fever and chills antedating the osteomyelitis should suggest the possibility of septicemia with metastatic involvement of the bone. A careful search must be made for a primary infection of the parapharyngeal space.

*Meningitis*—Involvement of the central nervous system may occur in the course of postanginal sepsis and suggest primary meningitis or meningoencephalitis.<sup>7b</sup> The diagnosis rests on a careful clinical examination plus studies of the blood and the spinal fluid.

#### TREATMENT

The treatment is surgical intervention. This must come early, before the development of metastatic abscesses in the viscera. Because time is so important, exploratory incision with the region under local anesthesia is indicated if the diagnosis is doubtful. It is generally agreed that the parapharyngeal space should be drained externally and the jugular vein ligated or excised,<sup>41</sup> although recovery has occurred by drainage of the abscess without ligation or resection of the vein.<sup>2b</sup> Some observers have expressed the belief that tonsillectomy should be performed in addition to the operation on the neck.<sup>42</sup> In the cases reported in this paper tonsillectomy proved life saving, probably because the abscess was either drained or removed by this procedure.

Chemotherapy as a supplement to surgical treatment may be of value in combating this condition.

#### CONCLUSIONS

Postanginal sepsis is a definite clinical entity that demands early diagnosis and operation to prevent death. This disease is due to suppurative inflammation of the internal jugular vein or of one of its tributaries. The possibility that it is present must be considered in every case of septicemia of unknown origin. The diagnosis is easy to make if the following sequence of events is considered: (1) An infection of the throat has occurred, according to the history or evidence from examination, (2) a state of septicemia or pyemia has developed. A latent period may or may not have elapsed between the infection and the time of onset of sepsis. A definite diagnosis may be made on finding tenderness, swelling or induration of the neck in a patient presenting the characteristic clinical picture, provided all other causes for sepsis are first ruled out. Swelling of the lateral wall of the pharynx or displacement or swelling of the tonsil may be additional evidence of this disease, but the absence of these signs is of no diagnostic importance.

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41 Mosher<sup>1</sup> Beck<sup>6b</sup> Claus<sup>26b</sup> Claus<sup>29</sup>

42 Beck<sup>3a</sup> Beck<sup>9a</sup> Claus<sup>26b</sup>

may occur in the absence of endocarditis as a result of fever or anemia. In such instances, as in case 1, the presence of severe septicemia and a functional cardiac murmur may lead to the incorrect diagnosis of acute bacterial endocarditis. The differentiation between septic phlebitis of a vein of the neck and acute bacterial endocarditis may be extremely difficult. A recent infection of the throat may antedate both conditions. The development, however, of embolism or of a murmur pathognomonic of valvular heart disease points to acute bacterial endocarditis.<sup>37</sup> The development of tenderness or swelling of the neck, as in the reported cases, may be the only clue to postanginal sepsis. If the condition is unrecognized, bacteria entering the general circulation may produce acute bacterial endocarditis.<sup>38</sup>

Fever, chills, *St. viridans* septicemia, a palpable spleen, secondary anemia, the presence of red blood cells in the urine and a systolic murmur may be noted in a patient with postanginal sepsis and may simulate subacute bacterial endocarditis. It is well known that a cardiac murmur does not necessarily point to the diagnosis of subacute bacterial endocarditis, although the absence of a murmur is strong evidence against such a diagnosis. Subacute bacterial endocarditis is differentiated from postanginal sepsis by the presence of chronic valvular or congenital heart disease and embolic phenomena.

*Acute Renal Infections*—Pain and tenderness in the loin may occur in a patient with postanginal sepsis as a result of metastatic abscess and may suggest acute pyelonephritis or carbuncle of the kidney. The urine reveals acute pyelonephritis if this is present. A history of fever or chills antedating the pain in the loin is suggestive of general sepsis with metastatic involvement of the kidney rather than of a primary abscess of the kidney.

*Blood Dyscrasia*—A sudden onset of sore throat, septic fever, chills, marked prostration and an edematous or ulcerative lesion of the tonsil or throat may occur with acute leukemia or agranulocytic angina and may simulate a primary infection of the throat with sepsis. Septicemia, on the other hand, may be associated with a leukemoid reaction or a state of marked leukopenia that may be confused with a blood dyscrasia. The correct diagnosis will rest on the clinical examination plus a study of a blood smear. Although myelocytes are common in sepsis, most of the white cells are metamyelocytes and mature polymorphonuclears, in contrast with the blood picture of acute leukemia, in which most of the cells are myeloblasts, with an occasional myelocyte present.<sup>39</sup> In overwhelming sepsis the bone marrow may be depressed to the point of leukopenia but rarely to that of agranulocytosis.<sup>40</sup> Differentiation between the agranulocytosis of sepsis and true agranulocytic angina may be difficult or impossible if the patient is seen late in the course of the disease. In sepsis the signs and symptoms of infection precede the fall in the white blood cell count. In agranulocytic angina the reverse is observed.

*Acute Osteomyelitis*—Acute osteomyelitis may be secondary to septicemia associated with phlebitis of the internal jugular vein. If the signs and symptoms of osteomyelitis dominate the clinical picture, the infection of the neck may be com-

37 White, P. D. *Heart Disease*, ed. 2, New York, The Macmillan Company, 1931, p. 344.

38 Artuse, C., cited by Abt.<sup>2a</sup>

39 Kracke, R. R., and Garver, H. E. *Diseases of the Blood and Atlas of Hematology, with Clinical and Hematologic Descriptions of the Blood Diseases Including a Section on Technics and Terminology*, Philadelphia, J. B. Lippincott Company, 1937.

40 (a) Bigler, J. A., and Brennemann, J. Sepsis with Leukopenia (Agranulocytosis) in Children, *Am J Dis Child* 40:515 (Sept.) 1930. (b) Jackson, H. Agranulocytic Angina and Allied Conditions, *Internat Clin* 3:68 (Sept.) 1933.

## Hemorrhagic Disorders and Blood Coagulation

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The number of important investigations on hematologic subjects recently reported is surprising in view of wartime conditions. Many of the contributions, of course, relate to work undertaken and largely completed before the entrance of the United States into World War II, but there is abundant and gratifying evidence that, in spite of necessary curtailments, significant research continues to be carried on in many centers throughout the country.

Of special interest are reports from Great Britain indicating a relationship between diminished hemoglobin in women and children and restrictions of diet imposed by present conditions. It should be appreciated that anemia in such conditions is likely to be but one manifestation of the impaired nutritional status and the situation presents a challenge to medical and public health authorities to provide instruction relative to securing adequate amounts of essential nutrients from available food materials.

## PERNICIOUS ANEMIA AND RELATED MACROCYTIC ANEMIAS

A number of important papers dealing with pernicious anemia appeared during 1942. Of these, the most significant is that of Fox and Castle,<sup>1</sup> who report that in human beings the intrinsic factor is secreted by the glands in the fundus of the stomach rather than chiefly by those in the pyloric region, as in swine. Other articles of special interest which deal with various aspects of pernicious anemia and other macrocytic anemias are concerned with the relation of solar radiation to the incidence of pernicious anemia, the chemical composition of the antipernicious-anemia factor in liver, the changes in the bone marrow, the relation between pernicious anemia and cancer of the stomach, the spontaneous occurrence in monkeys of a condition simulating subacute combined degeneration of the spinal cord, the presence of hypoprothrombinemia in pernicious anemia, the

1 Fox, H. J., and Castle, W. B. Observations on the Etiologic Relationship of Achylia Gastrica to Pernicious Anemia. Difference in Site of Secretion of Intrinsic Factor in the Hog and in the Human Stomach, *Am J M Sc* **203**:18 1942

# Progress in Internal Medicine

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## BLOOD

A REVIEW OF THE RECENT LITERATURE

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of the gastrointestinal tract to the development of pernicious anemia. These attempts may be summarized as follows. In swine the intrinsic factor is localized to the cardiac, pyloric and duodenal regions, and the cells concerned are designated as the "pyloric gland organ" by Meulengracht. Sufficient investigation has not been made of the intestinal tract as a site for the interaction of the intrinsic and extrinsic factors and the absorption of the product thus formed. On the other hand, it is recognized that in patients with pernicious anemia the fundus of the stomach is the chief site of the pathologic changes in the mucous membrane. Finally, it is stated that even removal of the entire region assigned to the intrinsic factor and the distal part of the intestine in dogs has not produced pernicious anemia in these animals. It is also noted that resections of the stomach and duodenum in man give rise to this form of anemia only in exceptional cases. In an effort to obtain new information, various areas of the hog stomach were resected, and after a considerable period the liver was removed and a liver extract prepared. This was administered to patients with pernicious anemia, in an assay of potency. The authors found that total gastrectomy performed on swine eleven months previously brought about a complete absence of the antipernicious-anemia principle in the liver. In 3 animals selective resection of the fundus caused, in periods of one hundred and sixteen, two hundred and fifty-eight and three hundred and seventy-nine days, a reduction or a complete loss of the principle. The authors consider that they have demonstrated a relationship between the fundus of the stomach and the amount of the specific principle in the liver in swine. It is their opinion that this is concerned with the utilization of the extrinsic factor by the organism.

Petri, Jensenius and Thyssen<sup>6</sup> conclude, after extensive experimental studies on dogs, that operative elimination of the pyloric and Brunner gland area in the duodenum, thought by some to be the sites in which the intrinsic factor is elaborated, did not result in experimental pernicious anemia. It did cause a severe pellagious symptom complex in young dogs and a mild subpellagrous condition in older animals. In addition, resection of the pyloric region, the Brunner gland region and the distal two thirds of the small intestine in 3 pups did not produce a regular state of pernicious anemia. On the other hand, these pups showed arrest of growth, emaciation, alterations in the skin and the hair and degenerative changes in the nervous system. In 2 of the 3 animals there appeared hyperchromic macrocytic anemia and attacks of diarrhea. It was the authors' conclusion that pernicious anemia was not produced, because (1) the operative procedure did not jeopardize the formation of the intrinsic factor (2) it was not sufficiently extensive and (3) the prevailing conception of the intrinsic factor and of the way in which the liver principle is formed is erroneous.

Olivia and Pitzurra<sup>7</sup> fed a patient with pernicious anemia 100 Gm of raw chopped beef and removed it from the stomach after one hour. Subsequently the patient responded adequately to the therapeutic test of intramuscular liver extract. The stomach content thus obtained was brought to a pH of 7.5, incubated and filtered, and was then administered to a second patient with pernicious anemia. This patient showed lessening of the diarrhea, diminution of the glossitis and a

6 Petri, S., Jensenius, H., and Thyssen, E. Experimental Studies on Production of Pernicious Anemia by Operation on the Digestive Tract. Results of Combined Elective Resection of the Pylorus and the Brunner-Gland Section of the Duodenum and the Distal  $\frac{2}{3}$  of the Small Intestine (on Pups), *Acta med Scandinav* **107** 532 1941.

7 Olivia, G., and Pitzurra, M. Reticulocytenfordende und antiperniziose Wirkung der Komplexe, "perniziöser Magensaft Fleisch" in Krankheitsfällen von perniziöser Anämie. *Klin Wchnschr* **21** 733, 1942.



advantages of the intramuscular treatment and the tendency to prolong the interval between maintenance doses to four weeks or longer, the relation of a deficiency of vitamin C to relapse in patients with pernicious anemia during the spring months, the possibility that polycythemia may result occasionally from liver therapy, in general, the failure of methods for the assay of liver extracts, except that of administering them to patients with pernicious anemia, and the illuminating studies on the cause of the disease which have been developed since Castle's earliest contributions

*Etiology*—(a) Role of Changes in the Gastrointestinal Tract Fox and Castle confirm the observations of Meulengracht,<sup>2</sup> of Magnus and Ungley<sup>3</sup> and others that desiccated portions of the fundus of the hog stomach were devoid of antipernicious-anemia activity, whereas those of the pyloric region displayed it. Furthermore, they obtained supporting evidence that the distribution of the material with blood-forming activity coincides with the site of secretion of the intrinsic factor. Their studies on the hemopoietic effect of desiccated human stomach led to the important conclusion that there is in the latter a distinctly different distribution of the active substance as compared with that in the hog stomach. Thus, preparations of the so-called fundic and cardiac areas of the human stomach were highly effective, whereas that of the pyloric area was only weakly active. This led the authors to conclude that in man, not the pyloric region of the stomach, but the areas designated as the "fundus" and the "cardia," are the important sites of the formation or secretion of the intrinsic factor. In their minds there is no question that in the human stomach it is the type of gland that is found in the fundus that is associated with antianemia activity. This observation is important, since it is in accord with the observation that in cases of pernicious anemia the fundus of the stomach undergoes degeneration. Furthermore, if the "pyloric gland organ" is not an important site of the formation of the intrinsic factor, it is readily understood why the blood picture of pernicious anemia does not develop following partial resection of the stomach in human beings, and why the pure duodenal secretion in man does not contain detectable amounts of the intrinsic factor.

Cox,<sup>4</sup> in a study of the stomach in 6 cases of pernicious anemia in which necropsy was performed, found extensive changes in the mucosa, similar to those described in this disease by Meulengracht and others. These alterations were sharply delimited from the pyloric zone and could be distinguished from other types of "gastritis." The changes suggested injury to the specific secretory cells of the body and fundus of the stomach, with repair by less differentiated epithelial cells. According to the author, there was no evidence of a return to normal in the cases in which there had been prolonged therapy. In 1 case of sprue significant gastric lesions were not shown. It was concluded that the gastric changes in pernicious anemia were not the result of the anemia but may have represented a true etiologic relationship.

It is stated by Petri, Bing, Nielsen and Kjerbye<sup>5</sup> that various attempts have been made to determine the etiologic relationship of the status of different parts

2 Meulengracht, E. Histologic Investigation into Pyloric Gland Organ in Pernicious Anemia, *Am J M Sc* **197** 201, 1939

3 Magnus, H. A., and Ungley, C. C. Gastric Lesion in Pernicious Anaemia, *Lancet* **1** 420, 1938

4 Cox, A. J. The Stomach in Pernicious Anemia, *Am J Path* **18** 782, 1942

5 Petri, S., Bing, J., Nielsen, E., and Kjerbye Nielsen, A. Deficiency of Anti-pernicious Anemia Principle in Liver Extract from Swine After Elective Resection of Fundus of Stomach. Clinicotherapeutic Study, *Acta med Scandinav* **109** 59, 1941

many of the changes in the blood are conditioned by states of the digestive system and that, on the other hand, the digestive system may be influenced by the composition of the blood

Joll and Adler<sup>11</sup> give a brief review, with a report of 2 cases of long survival after total gastrectomy, which is of interest relative to the role of the stomach in the etiology of pernicious anemia. The article deals with 135 reported cases of total gastrectomy, which is defined rigidly as removal of the whole stomach so that in the specimen are found a portion of esophagus at one end and a portion of duodenum at the other. Such a concise and precise definition surely offers no possibility of misunderstanding. Such cases are of special interest because the operation produces in many respects an ideal experimental situation in which to evaluate the relation of the stomach to addisonian pernicious anemia. Yet, as Chester Jones said in his admirable review on this subject, published in 1940, "the development of serious anemias is not to be feared. An occasional macrocytic or microcytic anemia ensues in the course of months." Jones concluded, according to these authors, that extragastric lesions must coexist for the production of addisonian pernicious anemia following total gastrectomy, possibly due to the destruction of argentaffin cells in the duodenum, small intestine, colon and appendix. Furthermore, in Jones's opinion an adequate and well balanced diet should suffice to prevent occurrence of anemia. With improved surgical technic and skill, it is likely that in the future complete gastrectomy will be performed successfully in an increased number of cases. In all such cases careful studies of the blood should be done, including hematocrit determinations, in order that, among other estimations, the cell volume may be determined at intervals. Now that Fox and Castle have demonstrated that the cells secreting the intrinsic factor are probably in the fundus of the stomach, it would be logical to expect that total gastrectomy would be followed by macrocytic anemia. There must be attached to this statement, however, some qualifying provisions. Such anemia should develop, provided the patient survives long enough and provided no other portions of the gastrointestinal tract can assume in totality the anti-pernicious-anemia function of the glands of the fundus. It has been shown that the duodenal secretion does not contain the intrinsic factor and that any activity in the ileum is in all probability due to the erythrocyte-maturing factor retained in the walls of the small intestine while it is en route to being absorbed by the portal system. The relatively brief period of survival following total gastrectomy is probably the greatest deterrent to the development of macrocytic anemia. In the reported cases the average duration of life is well under two years, and almost all patients die of metastases. The 2 patients whose cases are presented by the authors survived three years and two months, and three years and six months, respectively. Each had, both before and after the operation, moderately severe anemia, which appeared to be of the type associated with chronic hemorrhage rather than pernicious anemia.

A comprehensive discussion of achlorhydria and its ultimate significance is given by Crohn,<sup>12</sup> but reference will be made here only to that part concerned with the relation of achlorhydria to pernicious anemia. He emphasizes that at any decade of life a certain percentage of the normal population has achlorhydria, the incidence begins in childhood and increases with each decade up to the age of 60 years. He states that there is no explanation for this finding at present.

11 Joll, C. A., and Adler, D. I. Long Survival After Total Gastrectomy. A Brief Review, with a Report of Two Cases, *Brit. M. J.* **2**: 632, 1942.

12 Crohn, B. B. Achlorhydria. Its Ultimate Significance, *Tr. A. Life Insur. M. Dir. America* **28**: 74, 1942.

striking increase in the reticulocytes of the circulating blood. The marrow showed no changes. A second patient who received a similar injection improved, but not so strikingly. It was assumed that the reaction between the gastric juice of a patient with pernicious anemia and meat did not produce the active anti-pernicious-anemia principle but that it did result in the formation of something which stimulated a reticulocyte rise. The authors conclude that there are two distinct physiologic substances which stimulate erythropoietic functions, one for the formation of red blood cells and the other for the production of reticulocytes.

Crandall,<sup>8</sup> in an article dealing primarily with the effects of the absence of bile from the gastrointestinal tract, makes the rather startling claim that by the establishment of a bile fistula he is able to produce a macrocytic type of anemia resembling pernicious anemia in many respects. According to him, the blood picture is of the macrocytic, hyperchromic type, it is associated with hyperplasia of marrow erythroblasts, it shows a response to parenteral injection of liver extract, and, finally, it shows no response to any substance or dietary factor other than that which is effective in pernicious anemia. It is his opinion that an absence of bile from the gastrointestinal tract produces a deficiency of the anti-pernicious-anemia factor in the body because of a failure of absorption of this substance. These statements are important because, if confirmed, they indicate that a type of anemia has been produced in the dog which closely resembles pernicious anemia in human beings.

A brief but accurate and well presented resume of the role of the stomach in the etiology of pernicious anemia is given as an unsigned leading article in the *British Medical Journal*.<sup>9</sup> After stating the essential facts of the historical development of knowledge in this field, the author comments favorably on the work of Fox and Castle,<sup>1</sup> in which the apparent discrepancy between the anatomic and the biochemical changes in the stomachs of patients with pernicious anemia is explained. It is remarked that the work of these investigators has shown that there is no discrepancy but "that the mistake lay in the unnatural identification of pigs with men," which in this instance, at least, was unjustifiable. It is very properly emphasized again that an inference is dangerous when drawn from one species and applied to another. The article shows the difficulties with which investigators in this field are forced to contend, owing to the fact that they are confined to work on human subjects with the disease. It is considered by the author that work bearing on the mechanism of pernicious anemia has languished during the past five years for at least four reasons: lack of a suitable animal for experimental work, lack of a laboratory test for the liver principle, the relatively intractable nature of the materials in which the intrinsic and extrinsic factors are located, and the doubt whether the liver principle can be elaborated by interaction of the intrinsic and extrinsic factors in vitro.

Weiss and Foldes<sup>10</sup> give an extensive and detailed discussion concerning the interrelationship between the digestive system and the morphologic picture and the chemical composition of the blood, with the greater amount of emphasis on the latter. A schematic arrangement is presented which shows the many changes of the blood found in association with changes in the functional and organic state of the gastrointestinal tract, the liver and the pancreas. It is emphasized that

8 Crandall, L. A., Jr. Effects of Absence of Bile from Gastrointestinal Tract, *Memphis M J* **17** 114, 1942.

9 The Stomach in Pernicious Anemia, editorial, *Brit M J* **1** 765, 1942.

10 Weiss, S., and Foldes, E. The Digestive System and the Blood. Interrelationship Between the Digestive System and the Morphologic and Chemical Composition of the Blood, *Internat Clin* **1** 234, 1942.

para-aminobenzoic acid, melanin, insulin, estriogen and androgen are all composed chemically of benzene or aromatic rings, and he suggests that these substances are dependent for their formation on adequate production of dihydroxyphenylalanine through the agency of solar radiation

(c) Studies on the Active Principle of Liver Karrer<sup>16</sup> prepared a concentrated liver extract in an attempt to isolate the active principle and reports his studies on the composition and the characteristics of this principle. His method consists in extraction with 99 per cent ethyl alcohol followed by 50 per cent acetone. The latter is evaporated in vacuo, the proteins are precipitated with sulfosalicylic acid and the active principle is extracted with phenol. This impure preparation is then adsorbed on charcoal, washed with phenol five times and shaken with 75 per cent acetone. The active principle is found in the acetone-insoluble fraction. The pentose content is decreased, and repetition of the treatment with acetone results in a pentose-free substance. Further impurities are extracted with water-free pyridine. The material thus prepared was highly potent when tested clinically. Treatment with acetone of different concentrations or with ammonium sulfate did not fractionate it further. The preparations were not homogeneous, as was indicated by absorption spectrums, molecular weight analyses and determinations of the coefficients of dialysis through a membrane. Elementary analysis showed the following composition: carbon 45.6 per cent, hydrogen 6.7 per cent and nitrogen 14.6 per cent. The ninhydrin reaction was strongly positive, and the biuret test was weakly positive. The amino nitrogen content was 0.75 to 0.9 per cent, sulfur was present, but there was no pentose, protein or pterin. Following an eighteen hour hydrolysis with 20 per cent hydrochloric acid at 100 C, the amino nitrogen content increased to 9 per cent, and the original amino nitrogen content was doubled by trypsin and chymotrypsin at a  $p_H$  of 7.7 in thirty-eight hours. Pepsin in five-hundredth normal hydrochloric acid did not increase the amino nitrogen. The preparations were found to contain arginine and tyrosine but no phenylalanine, proline, hydroxyproline, glycine, tryptophane or histidine.

In 1935 Erdos,<sup>17</sup> now of the staff of the National Polytechnical Institute of Mexico, D. F., isolated from 1 Kg. of liver 5.8 Gm. of a yellowish brown powder as a silver salt. In this he discovered the presence of three free COOH groups and eighteen -CO-NH- groups and deduced a molecular weight of approximately 10,000. Four years later<sup>18</sup> he initiated new experiments, which form the basis for his present report. By acid aqueous extraction, treatment with barium hydroxide, concentration in a vacuum, addition of 99 per cent alcohol, filtration, reconcentration and precipitation with a solution of silver nitrate, he obtained a new silver salt having the following composition: carbon 67.50 per cent, hydrogen 6.40 per cent, oxygen 4.60 per cent, total nitrogen 14.40 per cent, amino nitrogen 1.40 per cent, sulfur 0.99 per cent, phosphorus 1.06 per cent, silver 5.04 per cent. One kilogram of liver yielded 2.09 Gm. of the substance, "which was extraordinarily active in clinical tests." For an approximate estimate of potency, the fractional precipitation with the alcohol test of Schales<sup>19</sup> and the author's own biologic test (based on the influence of the substance to be tested

16 Karrer, P. Versuche zur Reinigung des Antiperniziosa-Faktors, Schweiz med Wchnschr **71** 343, 1941

17 Erdos, J. Die Bewertung von Leber- und Magenpräparaten. Biochem Ztschr **277** 342, 1935

18 Erdos, J. The Chemical Composition of Liver Preparations. Science **96** 141, 1942

19 Schales, O. Einfaches Laboratoriumsverfahren zur vergleichenden Leberkonzentrationsprüfung, Klin Wchnschr **16** 277, 1937

No histologic abnormality is present to account for the achlorhydria which is found in an average of 5 per cent of the population. He regards anacidity as asymptomatic except in a very small percentage of these persons, in whom it may cause diarrhea. He believes that complete anacidity, or achylia gastrica, is an essential part of the syndrome of pernicious anemia but concedes that "occasionally" one meets with a patient who has persistent secretion of hydrochloric acid. We are not in accord with this statement, for we regard the so-called pernicious anemia in a patient with hydrochloric acid in the gastric secretions as due to some cause other than deficiency of the intrinsic factor of Castle. In the opinion of Crohn the achlorhydria in patients with pernicious anemia is associated, in most instances, with true atrophic gastritis, which does not change when a remission is induced by anti-pernicious-anemia medication. In his opinion, insufficient data are at hand to say how many patients with asymptomatic achlorhydria will ultimately have some type of anemia. He warns that if a person has anacidity and has a blood relative with pernicious anemia, the situation constitutes an added risk from the standpoint of insurance. With the uncertainty as to whether a person with achlorhydria will have pernicious anemia, and with available potent therapy, such a risk is surely not a great one, and moreover any conclusion in regard to it should be based on a study of the length of life of patients with pernicious anemia and of the longevity of their blood relatives. Certainly, from a theoretic standpoint there is no reason why a patient with pernicious anemia should not survive for the normal span of life.

McGowan<sup>13</sup> gives an extended review in which he discusses some controversial points concerning the etiology of pernicious anemia and allied conditions, the nature of the changes in the marrow and the circulating blood, and the relation of subacute degeneration of the spinal cord to the disease.

(b) Influence of Solar Radiation. It had previously been claimed by Smith<sup>14</sup> that there was a significant relation between a relative lack of solar radiation and the mortality from pernicious anemia in the United States prior to the therapeutic use of liver. Apperly<sup>15</sup> warns that before accepting such a conclusion one should take into account that various additional factors may have determining effect. Among others, he names altitude, dust, various individual and racial differences, and possibly unknown conditions. The author considers that the relation between pernicious anemia and solar radiation might be more accurately shown by an attempted correlation of this disease with some other human malady which has a known relation to exposure to the sun's rays. With this in mind, the mortality from pernicious anemia before the modern treatment was introduced has been compared with the mortality from cancer of the skin in the various states of this country. A consideration of the collected data leads the author to conclude that the incidence of cancer of the skin (corrected for other causes than exposure to sunlight) has an inverse relation to that of pernicious anemia. This lends support to Smith's contention that the incidence of this variety of anemia is related inversely to the amount of solar radiation. The author reminds us that there is a relatively high incidence of pernicious anemia in blond and prematurely gray-haired persons, who are often of a eunuchoid type, and that the disease is often associated with diabetes. He emphasizes that argentaffin granules,

13 McGowan, J. P. *Pernicious Anaemia: Some Vital Considerations*, Edinburgh M. J. **49** 568, 1942.

14 Smith, J. H. *The Relation Between Deficiency of Solar Radiation and Mortality Due to Pernicious Anemia in the United States*, Am. J. M. Sc. **188** 200, 1934.

15 Apperly, F. L. *The Relation of Pernicious Anemia to Solar Radiation and Skin Cancer*, Am. J. M. Sc. **203** 854, 1942.

that the maintenance requirements vary widely in different patients. From a practical standpoint, they do not consider a single red blood cell count, the Pince-Jones measurement of the red blood cells or the estimation of the mean corpuscular volume as feasible types of information for the guidance of the physician. Their recommendations are as follows: (1) If the red blood cell count is persistently under 4,000,000 per cubic millimeter, 30 to 75 U S P units of liver extract should be given weekly for two or three months, and if this augmented dosage results in higher blood values, one is justified in concluding that the previous dosage was inadequate, (2) if glossitis or unfavorable progression of the neural symptoms occurs, regardless of the high level of the red blood cell count, the treatment must be considered inadequate, (3) if the patient regains a feeling of better health when, unknown to him, he is receiving a larger amount of extract, the original treatment must be regarded as suboptimal. It is important from a practical standpoint to note that when in the 80 patients the interval between the intramuscular doses of 15 U S P units was from one to four weeks, there was no change in the blood level and there was no neural relapse. This suggests strongly that the anemia of the average patient can be controlled on such a dosage. Nevertheless, the authors state clearly that probably certain patients require more liver extract than this amount, particularly in the presence of infection or of severe damage to vital organs.

Della Vida and Dyke<sup>22</sup> comment on their experience in the treatment of patients for pernicious anemia by intramuscular injections of liver extract, stating that only at the beginning of therapy are weekly doses given, thereafter, the great majority of patients are maintained satisfactorily on doses given once every two or three months. They administer a dose of 4 to 6 cc of fully potent liver extract. Widely varying dosages of liver extract are used in the treatment of pernicious anemia, owing partly to custom and partly to the employment of extracts of low potency, according to these authors. In an effort to establish new criteria of potency, a series of 125 cases of pernicious anemia were reviewed, and the relation between the red blood cell count before, and its increase during, the first two weeks of parenteral injection of liver extracts has been expressed by mathematical equations. It was concluded that in a majority of the cases the response exceeded that anticipated from previously published formulas and that the red blood cell increase was more reliable in assaying the potency of liver extracts than the reticulocyte response. The formula  $I 0.93 - 0.214 E_0$  (in which  $I$  is the average weekly increase in red cells during the first two weeks of treatment and  $E_0$  is the red cell count before treatment) has been found to express a satisfactory response to treatment and is proposed as the standard equation for the assay of the potency of liver extracts. Following this article is a note by Dyke on the dosage of liver extract, in which he refers to the action of the Anti-Anemia Preparations Advisory Board of the United States Pharmacopeia and states that their units are based on the red blood cell count and the reticulocyte response. In his opinion the assay should be based entirely on the increase in the red blood cell count. Furthermore, he believes that units should not be utilized but the actual amount of liver necessary to produce a red cell response according to an accepted formula. We consider, after a thorough trial of the present U S P unit system, that it serves its purpose satisfactorily, and we see no objection to evaluating the potency of any given sample of liver extract by utilizing both the red blood cell and the reticulocyte increase.

<sup>22</sup> Della Vida, B. L., and Dyke, S. C. Maximal Response to Liver Therapy in Pernicious Anemia, with a Note on Dosage, *Lancet* 2:275, 1942.

on anemia induced with phenylhydrazine) were employed. Further, he states that the results were confirmed by the clinical test of the reticulocyte response. It was concluded that for the present the following ideas can be entertained concerning the chemical structure of the active fraction of liver extract. It is an amino acid complex with three free COOH groups, it contains sulfur and phosphorus, it is soluble in water, acids and bases precipitates with alcohol concentrations greater than 87 per cent and has a molecular weight of 6000.

*Treatment of Pernicious Anemia*—In regard to the treatment of macrocytic types of anemia Castle<sup>20</sup> makes the following comments. First that the conditions amenable to anti-pernicious-anemia therapy are true Addisonian pernicious anemia, the macrocytic anemia of pregnancy and, in certain rare cases, nutritional macrocytic anemia due usually to intestinal disturbances. With the exceptions just noted "all types of anemia fail entirely to respond to such preparations." He strongly advocates the use of preparations described in the United States Pharmacopeia or preparations accepted by the Council of the American Medical Association, the potency of which is defined in terms of official units. It is also emphasized that the most satisfactory form of anti-pernicious-anemia therapy is the intramuscular injection of a concentrated liver extract. The following reasons are given. The extract is from sixty to one hundred times as effective when administered parenterally as when given by mouth. A small volume, for instance 1 cc., containing 15 units, may be injected as infrequently as every two weeks to a month as a maintenance dose, the patient is less likely to discontinue the parenteral medication when the blood is normal, a certain unpredictable number of patients in severe relapse fail to respond adequately to oral medication, the neural manifestations are more amenable to this form of therapy. Although liver extracts contain various members of the vitamin B complex, it is Castle's opinion that these are nonessential to the success of the remission, and he considers their use in the treatment of pernicious anemia to be a waste of material. Although he admits that large amounts of whole or autolyzed yeast may cause improvement in patients with pernicious anemia, it is his belief that probably these agents act only indirectly through the power to form liver extract in the body. He concludes his remarks on therapy with the sound advice that the sole essential for maintaining continued and complete remission in pernicious anemia is the exhibition of sufficient amounts of active material by a single route at regular intervals. Finally, he questions the propriety of continuing to employ the adjective "pernicious" with reference to the disease, since the advances in therapy during the past fifteen years have almost deprived it of any meaning.

Strauss and his associates<sup>21</sup> have endeavored to clarify some of the problems incident to the use of liver extract in the treatment of patients with pernicious anemia. Their conclusions are based on observation of the blood levels of 80 patients who received liver extract in varying amounts and at different intervals over a period of five to nine years. As a result of their studies, they have adopted a uniform maintenance dose of 15 USP units of purified liver extract, injected every four weeks. In the eighteen months during which this plan has been in effect, no relapses have been encountered in the blood, the gastrointestinal system or the nervous system, either objective or subjective. They emphasize, however

20 Castle, W. B. Some Remarks on Therapy for Anemia, *New England J. Med.* **226** 903, 1942.

21 Strauss, M. B., and others. The Treatment of Pernicious Anemia. A Nine Year Study of Maintenance Requirements, with a Note on the Efficacy of Purified Liver Extracts in the Control of Neural Lesions, *New England J. Med.* **226** 1013, 1942.

had been observed. In most instances, desiccated stomach therapy had not been used in a sufficient number of patients to enable the observer to express an opinion as to its efficacy. Dilute hydrochloric acid was thought to be of little value, and arsenic congo red and choline were not considered helpful in the treatment of this disease. It is of interest that all of the contributors to the symposium favored the administration of iron, especially in the early stages of remission, when the red blood cells increase more rapidly in number than does the hemoglobin content of the circulating blood. Consequently, at this stage of therapy the color index commonly falls below 1. There may be a greater need for supplemental iron in Germany because of dietary deficiency.

Fullerton<sup>25</sup> assigns the responsibility for inadequate maintenance therapy in cases of pernicious anemia to those practitioners who are ignorant of the elementary therapeutic principles employed in treating the disease. According to him, maintenance treatment is frequently reduced to grossly insufficient dosages, or patients may even be advised that therapy is unnecessary as long as they feel well. He warns that such management may lead to progression of subacute combined degeneration of the spinal cord. He very properly advises his patients that treatment must continue throughout the remainder of life. He concludes by stating that if all practitioners realized the importance of adequate maintenance therapy the death rate from pernicious anemia would show a sharp decline. He emphasizes, furthermore, that treatment should be controlled by examinations of the blood.

Accurate diagnosis of blood disorders, based on the changes in the blood and on the clinical features, is emphasized by Vandersluis<sup>26</sup> as a prelude to the inauguration of therapy. He states that in making the diagnosis of pernicious anemia one should keep in mind macrocytosis, leukopenia with relative lymphocytosis, and megaloblastic hyperplasia of the marrow. The clinching proof of the identity of the disease is the reticulocyte response to liver therapy. The author is aware that the hematologic changes seen in pernicious anemia may occur in other conditions and accordingly reminds the reader that the diagnosis depends on the clinical features of the disease as well as on the laboratory findings.

Dyke<sup>27</sup> comments on the soundness of the order of the British government that only liver preparations suitable for injection will be made in England henceforth. He points out that the oral mode of administration is wasteful and that, even though preparations will be available for intramuscular injection, they should be administered judiciously. By this is meant that they should be given only to those patients whose disease has been established definitely as pernicious anemia by the utilization of all modern diagnostic methods, and to such patients in the minimum adequate dosage. Furthermore, a plea is made to establish in England a standard statement of the potency of the type of liver extract hidden under the trade name, especially now that a brand familiar to the physician may often be temporarily unobtainable.

Dyke, Della Vida and Delikat<sup>28</sup> have observed the tendency of patients with pernicious anemia to relapse during the spring of the year and attribute this to a deficiency of vitamin C. This conclusion is based on the successful treatment of

25 Fullerton, H. W. Pernicious Anaemia, *Brit. M. J.* **2** 291, 1942.

26 Vandersluis, C. Hematology of Pernicious Anemia. *Minnesota Med.* **25** 36, 1942.

27 Dyke, S. C. Husbanding of Liver Extracts, *Lancet* **1** 185, 1942.

28 Dyke, S. C., Della Vida, B. L., and Delikat, E. Vitamin-C Deficiency in "Irreversible" Pernicious Anaemia, *Lancet* **2** 278, 1942.



Askey<sup>23</sup> advocates, as the routine treatment for pernicious anemia an initial intramuscular injection of a massive dose of liver extract followed by monthly injection of doses sufficient to replenish the utilized material. He assumes that a normal human liver, weighing 1,500 Gm, stores approximately 125 to 225 U S P units and that this is apparently exhausted when the patient has severe anemia. This amount plus that needed by other body tissues in relapse should represent several hundred units. The procedure now used tentatively at the Los Angeles General Hospital is as follows. One cubic centimeter of a concentrated liver extract containing 15 U S P units, is administered intramuscularly. If there is no untoward reaction, the following day 9 cc is injected. This brings the total dose to 150 units. Thereafter, at monthly intervals a dose of liver extract containing 30 units is given. Vitamin B is not prescribed as it is thought that the vitamin needs are supplied by the liver extract and by a general diet. If the gastrointestinal symptoms persist after the blood returns to normal dilute hydrochloric acid is given but this has rarely been found necessary. Occasionally, in conjunction with the liver therapy, medicinal iron is administered.

A symposium on the treatment of pernicious anemia is given<sup>24</sup> by a group of the leading internists of Germany, including Heilmeyer, of Jena, Nonnenbruch, of Frankfurt on the Main, Hoff, of Giaz, Schilling, of Rostock, Bingold, of Nuremberg, and Buding, of Berlin. As their opinions concerning the various aspects of therapy are much in accord, no attempt will be made to record individual statements. In general, it was agreed that the intramuscular injection of liver extract is the best form of therapy. Usually a preparation corresponding to a purified solution of liver U S P was given in doses of 2 to 4 cc every two to four weeks. Some patients were treated as often as once a week, others especially those who did not return for observation at regulation intervals were given 'depot injections', i e, 5 to 10 cc of a potent liver extract was injected intramuscularly every four to six weeks. The fact that no test animals are available makes the greatly desired standardization of liver preparations for parenteral use impossible, and consequently, as one contributor said, "the patient himself must be the test object." In no instance was a patient with uncomplicated pernicious anemia found to be refractory to potent therapy. It was said, however that vitamin deficiency might inhibit the anticipated response. The maintenance dose of liver extract was considered to vary greatly with different patients, just as does the dose of insulin for patients with diabetes mellitus. One patient who stopped therapy had no relapse for a year and a half. That is unusual, but the example serves to illustrate that the maintenance dose is not the same for all patients. It was generally agreed that an increased amount of therapy is required by older patients and by those in whom infection develops. The injection of an excess of liver extract is not regarded as a waste, for any amount over immediate demand is stored in the body and utilized when needed. The results in the subacute combined degeneration of the cord are not as striking as in the anemia, but in all instances the process is arrested and in some a remarkable improvement occurs. Usually, large doses of liver extract are injected, in combination with parenteral injections of vitamin B<sub>1</sub>. One contributor advised that 4 cc be injected intramuscularly daily for weeks, in combination with parenteral injection of vitamin B<sub>1</sub>. There was uniform agreement that no case of the achrestic anemia of Wilkinson

23 Askey, J. M. Pernicious Anemia. Adequate Versus Optimum Treatment, California & West Med **56** 72, 1942.

24 Heilmeyer, L., Nonnenbruch, W., and Fox, F. Die Bioerkmassigste Art der Behandlung der perniziösen Anämie, Med Klin **38** 169, 1942.

status of the gastric secretion bears any relationship to the development of polycythemia, with the single exception that so far as the blood values are concerned, pernicious anemia in relapse and polycythemia cannot coexist simultaneously

George R. Minot adds his comment, as follows

I do not think that patients with pernicious anemia will develop polycythemia with a return of free hydrochloric acid in the gastric contents

We wish to add that we are in entire accord with the statements of both Castle and Minot

Ferrary,<sup>32</sup> in a study of the erythemic response to liver therapy, presents the case of a 64 year old woman with pernicious anemia complicated with diabetes mellitus in whom there developed an excessive increase of red blood cells and hemoglobin after intramuscular administration of liver extract. This patient had been treated when in relapse, and her blood promptly returned to normal. After a period of approximately a year, however, during which time she had been given liver extract in doses of 10 U. S. P. units weekly, she was found to have a hemoglobin level of 131 per cent and an erythrocyte count of 10,650,000 per cubic millimeter. After the therapy had been omitted for about one month, the hemoglobin value was found to be 120 per cent and the erythrocyte count 6,250,000. Two weeks later the therapy was resumed, with doses of 10 units being given every three weeks, and after an interval of approximately eight months the hemoglobin was 100 per cent and the red blood cell count 5,050,000. According to the author, there are three possible explanations of the erythemoid reaction: (1) The administration of liver extract may have been continued through a period of spontaneous remission, (2) the patient's hemopoietic response may have been overstimulated by a relative overdosage of liver extract, (3) perhaps, associated diabetes produced the condition by dehydration and hemoconcentration. It is considered that, of these possibilities, the first is the most likely explanation, and hence it is his view that the erythemoid blood picture could not be reproduced without the assistance of a spontaneous remission. This case in our opinion is unique, as a similar one has not been observed by us in approximately fifteen years during which many patients have been treated, some with exceedingly large doses. Certainly, from a practical standpoint there is no danger of overtreatment, in fact, the great difficulty in the therapy of the disease is to guard against undertreatment. Whatever may have been the cause of the increased red blood cell count, in our opinion it probably was not related directly to liver extract therapy.

*Bone Marrow in Pernicious Anemia*—Davidson and his associates<sup>33</sup> have made a study of the changes observed in films prepared from sternal marrow in cases of pernicious anemia before, and at various short intervals after, the initiation of liver therapy. To obtain a working classification, they divided all erythroblastic marrow cells in Romanowsky-stained films into four types, differentiated chiefly by nuclear structure. For the detailed characteristics of the four groups, reference should be made to the original article. They observed that within six to ten hours after the initial injection of liver extract there is a reduction in the mean size of the predominant cells, accompanied by a striking alteration in the character of the nucleus. In other words, type II increases in frequency at the expense of type I, which is the most primitive type. After thirty-two to seventy-

32 Ferrary, P. B. Erythemic Response to Liver Therapy in Treatment of Pernicious Anemia, *J. M. Soc. New Jersey* **39** 19, 1942

33 Davidson, L. S. P., Davis, L. J. and Innes, J. The Effect of Liver Therapy on Erythropoiesis as Observed by Serial Sternal Punctures in Twelve Cases of Pernicious Anemia, *Quart. J. Med.* **11** 19, 1942

patients by the administration of vitamin C and continuation of exactly the same dosage of liver extract. The authors contend that the diet of the general population of England under war conditions is known to be deficient in this vitamin. According to them, even with ample dosage of liver extract hemopoiesis cannot be returned to normal in the face of a deficiency of vitamin C.

Cole<sup>29</sup> reports the case of a 3 week old infant who had pronounced macrocytic anemia with a red blood cell count of 2,650,000 per cubic millimeter and a hemoglobin value of 54 per cent. Normoblasts, megaloblasts and primary erythroblasts were present in the peripheral blood. Following a single intramuscular injection of liver extract, there was a reticulocyte rise to a maximum of 22.5 per cent on the seventh day after treatment, and eventually a complete hematologic and clinical recovery. It is suggested that the child began life with a deficiency of the anti-pernicious-anemia principle and that treatment with sulfapyridine (2-[paraaminobenzenesulfonamido]-pyridine) and sulfanilamide for a pulmonary infection may have been contributing factors.

Nutritional macrocytic anemia which responded to liver extract in an infant 4 months old is reported by Fouts and Garber<sup>30</sup>. The infant had suffered from vomiting, had refused to take food and had lost weight. It may be of importance that the mother during gestation had eaten no meat on account of previous toxemia of pregnancy. The red blood cell count was 910,000 per cubic millimeter. There was no response to iron, brewers' yeast and various preparations of the vitamin B complex. The mean corpuscular volume was 92 cubic microns. It was assumed that the macrocytosis was more pronounced prior to blood transfusions. Following the intramuscular injection of 0.25 U.S.P. unit of purified liver extract daily, the reticulocytes rose to a peak of 26.8 per cent. After three months of liver extract therapy, the child had gained approximately 5 pounds (2268 Gm.) in body weight, and the blood was normal. According to the authors, this condition is not common. It most frequently appears after an infection of the upper respiratory tract followed by vomiting or diarrhea or both. These patients are notably malnourished and fail to gain weight on change of formulas. Apparently, the anemia in this patient was due to inadequacy of the amount of extrinsic factor in the diet plus deficiency of protein intake in the mother during gestation.

Goldstein<sup>31</sup> by a search through the literature and by personal communications has investigated the question whether polycythemia may be induced by liver treatment in patients with pernicious anemia. The evidence accumulated was much against this possibility. The reply of W. B. Castle, of Boston, is the most complete answer to the inquiry, and it is quoted in full:

The only suspicion of erythrocytosis in connection with the therapy of pernicious anemia which I have observed is the occasional patient who, before the hemoglobin reaches a normal value, may have transiently a red blood cell count of  $5\frac{1}{2}$  to 6 million. I take it that this is not, however, polycythemia because of the normal or subnormal hemoglobin values.

I was very much interested in Birnie's report and consider that his patient represented a chance association between whatever factors make for polycythemia vera and whatever factors make for pernicious anemia. The remission produced in the pernicious anemia by adequate liver therapy allowed the polycythemia to express itself.

So far as I know, it is impossible to raise the red count or the hemoglobin above normal in normal individuals by liver extract or iron therapy, so that I consider it unlikely that the

29 Cole, L. Hyperchromic Anaemia in an Infant. Response to Liver Extract, *Lancet* 2: 759, 1941.

30 Fouts, P. J., and Garber, E. Nutritional Anemia in an Infant Responding to Purified Liver Extract, *Am. J. Dis. Child* 64: 270 (Aug.) 1942.

31 Goldstein, H. I. Pernicious Anemia Alternating with Polycythemia Polyglobulia, *Rev. Gastroenterol.* 9: 406, 1942.

ably to liver therapy whereas the anemia which is not associated with megaloblasts is refractory to this therapeutic agent. Israels<sup>37</sup> has recently identified seven different types of erythroblasts whereas Davidson and his associates divide these cells into four groups, but it is pointed out that perhaps it is sufficient for the clinician to know whether the marrow is predominantly megaloblastic or predominantly normoblastic or mixed in character.

Israels<sup>37</sup> in reply to several letters of criticism with regard to the diagnosis of pernicious anemia and with special reference to the clinical study of the marrow, emphasizes that in hematology, as in other fields of medicine, the diagnosis depends on a consideration of the whole picture as presented by all of the information available. He considers that the most important information obtained from the marrow with reference to the diagnosis of anemia is whether the marrow is hypoplastic, hyperplastic or about normal and whether it is megaloblastic or normoblastic. According to him, megaloblastic marrow occurs in pernicious anemia, in the refractory achrestic anemia and in certain types of nutritional anemia, such as that accompanying sprue. "Apart from these," he states, "in my extensive experience, normoblastic marrow is always present." He considers, therefore, that the total change in the marrow is of diagnostic importance. He does sternal puncture commonly, according to the following indications: any doubt about the diagnosis, such as a history of failure of liver therapy, unusual age or exceptional clinical signs or symptoms, grave anemia with an equivocal blood picture, and, finally, any case the subject of research about which the fullest information is desirable.

Wilson<sup>38</sup> gives a most comprehensive review of present knowledge of the marrow in anemia, including the historic aspects, and devotes considerable discussion to the changes which occur in pernicious anemia. He has described serial examinations of marrow in cases of pernicious anemia, the specimens being obtained during relapse, before treatment, in remission and again in an early stage of relapse. It is his conclusion that, following liver therapy, there is ripening of the abnormal megaloblasts, without the development of further megaloblasts. He is also of the opinion that there is initial temporary stimulation and then, later, lesser but more prolonged stimulation of the definitive normoblastic cells. He does not regard the abnormal granular cells present in pernicious anemia or the megaloblastic cells as representing a reversion to embryonic erythropoiesis. He concludes that a reappearance of the megaloblasts during a relapse is due to megaloblasts which have persisted in the marrow in numbers too small to be detected in aspirated material. The megakaryocytes are reduced in number in the marrow of patients with pernicious anemia who are untreated either during relapse or during remission. His observations of the marrow of patients with subacute combined degeneration of the spinal cord in whom there was no anemia indicated that the only abnormality present was the "giant stab forms." He suggests that possibly these may represent the initial change in the marrow in patients with pernicious anemia.

Dacie,<sup>39</sup> in discussing the diagnosis of pernicious anemia by means of sternal puncture, states that it is exceedingly difficult to distinguish between megaloblasts and primary erythroblasts. He believes that they merge imperceptibly into each other. However, he finds the following working hypothesis helpful. Megaloblasts are considered to be primary erythroblasts of varying maturity which because

37 Israels, M. C. G. Diagnosis of Pernicious Anaemia, *Lancet* **1** 487, 1942.

38 Wilson, T. E. Bone Marrow in Anaemia, *M. J. Australia* **1** 513, 1942.

39 Dacie, J. V. Diagnosis of Pernicious Anaemia, *Lancet* **1** 520, 1942.

two hours the change is still more pronounced, as the picture is dominated by the even more mature type III cells. In other words, the megaloblastic picture becomes normoblastic. The authors are inclined to believe that the mechanism underlying the widespread cellular change is a direct physicochemical process due to the action of the liver extract, rather than cellular mitosis. They believe also that the rapidity of the change from a megaloblastic to a normoblastic marrow supports the view that normoblasts can be derived directly from megaloblasts. Furthermore, they consider that they have collected evidence from a study of the sternal marrow in cases of severe untreated non-deficiency anemia and hemolytic anemia which suggests that under severe and prolonged strain the normoblastic may revert toward the megaloblastic blood picture. If this occurs according to the authors, it is additional evidence that megaloblasts and normoblasts belong to one developmental series.

In a letter to the editor of the *Lancet*, Davidson, Davis and Innes<sup>34</sup> urge that the clinician who is not engaged in research in hematology rely on intelligent studies of the peripheral blood as his diagnostic mainstay in dealing with various diseases of the blood rather than on a study of the sternal marrow. They contend that sternal puncture is necessary only in the occasional cases in which anemia fails to respond to adequate doses of liver extract or in which purpura or leukopenia is an unexpected presenting feature. Furthermore in such cases a helpful interpretation of the marrow can be given only by those who have had considerable experience in such work. It is emphasized also that the diagnosis of pernicious anemia and of other disorders of the blood is not made on the presence or the absence of any particular cell type, such as the megaloblast, but on the frequency distribution of the various cells constituting the marrow. In the same issue of the *Lancet* is a communication by Murray,<sup>35</sup> who likewise states that pernicious anemia can be, and still is, diagnosed by physicians who recognize the clinical picture and call on the pathologist to confirm it by an interpretation of the blood picture. He infers, and very properly in our minds, that a complete examination of the blood, with a halometer reading, followed by a reticulocyte count made after an adequate dose of a potent liver extract can confirm the diagnosis in most instances.

In an editorial review entitled "The Clinician and the Megaloblast,"<sup>36</sup> it is stated that the presence of the megaloblast in the blood and the marrow indicates a reversion to the embryonic type of formation of red blood cells. To the clinician, from the time of Ehrlich the megaloblast in the blood stream meant strong support for the diagnosis of pernicious anemia. After a lapse of some years, in 1927, the importance of the megaloblast in this disorder received renewed emphasis from the work of Peabody. This investigator observed that liver therapy caused a megaloblastic marrow to change rapidly into a marrow in which normoblasts and then mature erythrocytes predominated. His conclusion assumed logically that liver extract hastened the maturation of the red blood cells in the marrow. With the widespread use of the sternal puncture, a large amount of information has accumulated about this problem. It is now thought that there are two interchangeable series of erythroblasts—megaloblasts and normoblasts—which are derived from a common basophilic stem cell (proerythroblast). It is a common belief that the anemia associated with megaloblastic hyperplasia will respond favor-

34 Davidson, L. S. P., Davis, L. J., and Innes, J. Diagnosis of Pernicious Anaemia, *Lancet* 1 428, 1942.

35 Murray, D. S. Diagnosis of Pernicious Anaemia, *Lancet* 1 428, 1942.

36 The Clinician and the Megaloblast, editorial, *Lancet* 1 358, 1942.

tremor of the hands, spastic paraplegia affecting the hindlegs wobbling rapidly increasing ataxia with progressive diminution of power and finally complete flaccid paralysis of the hindlimbs and tail. The limb reflexes at first increased were absent in the final stages of the disease. Loss of sensation was a late symptom in most cases. The histologic picture of primary degeneration of the spinal cord in monkeys appears to be indistinguishable in its main features from that of subacute combined degeneration in man. The primary lesion is not sclerosis but true softening with fatty degeneration of the myelin sheaths and subsequent disappearance of the axis cylinders without any inflammatory gliosis. The histologic resemblance however, is no criterion for the belief that they are identical diseases. Much more comparative study must be done before the identity of the two conditions can be established. The possibility is mentioned that the disorder may arise from a vitamin deficiency. Suggestive evidence was obtained that a product equivalent to a purified solution of liver U S P containing vitamin A, B<sub>2</sub> and B<sub>12</sub> might be of real benefit in the condition.

The case of a man aged 24 with pernicious anemia and subacute combined degeneration of the spinal cord is presented and discussed by Ranson and Reback.<sup>43</sup> The neurologic condition was noted at a relatively early age, the response to therapy was remarkably good and there were some interesting hereditary features. The earliest manifestations of pernicious anemia appeared at the age of 22 years and those of subacute combined degeneration of the cord at 24 years. The latter developed despite oral liver therapy which did not keep the blood entirely within normal limits but in the vicinity of 4 000 000 red blood cells per cubic millimeter at least for part of the time. When first observed by the authors the young man was moribund, completely paralyzed in both legs and psychotic. After massive doses of liver extract and thiamine had been given parenterally followed by massage, passive and active exercises and as soon as feasible, reeducational walking exercises he improved remarkably. Four months after his discharge from the hospital he returned to work, discarded his cane and could walk as far as 14 blocks without difficulty. Sixteen months after discharge his gait appeared to be normal but it should be noted that there was persistence of hyperreflexia and of pathologic reflexes and that the vibratory and positional sense of the legs was still impaired. The authors suggest that the remarkable improvement was due to the parenteral administration of large amounts of liver extract and thiamine and to the early initiation and vigorous continuation of physical therapy and reeducational measures. The continued improvement they attribute in part to the maintenance of the patient's red blood cell count above 5 000 000 cells per cubic millimeter by intramuscular injection of appropriate doses of liver extract. We are in accord with these statements but would like to emphasize that one other aspect of this patient's illness was of favorable significance with reference to the changes in the spinal cord, namely that although he had experienced the symptoms of pernicious anemia for about two years, the changes in the spinal cord had been present for only about four months. Experience has shown that the duration of the neurologic manifestations bears a greater relation than does the extent of the changes to the degree of subsequent improvement. Another interesting phase of subacute combined degeneration of the spinal cord is emphasized by the aforementioned authors, namely the hereditary tendency which undoubtedly plays an important role in its etiology. They refer to previous publications by various authors who have reported the occurrence of subacute combined degeneration in

43. Ranson, S. W. Jr. and Reback, S. A Case of Subacute Combined Degeneration of the Spinal Cord with Interesting Hereditary Features. *Ann. Int. Med.* 17:779, 1942.

of retarded development, may receive hemoglobin at an unusually early age and thereby become polychromatic or orthochromatic. This quantitative change may be observed in all degrees of intensity according to the rates at which the cells develop and the stages of development at which the hold-up occurs. In patients with pernicious anemia in severe relapse, the maturation of the hemocytoblasts and of the early primary erythroblasts is arrested, and many of the nucleated cells containing hemoglobin are large and have relatively immature nuclei. In certain other obscure types of anemia the maturation is delayed at a later stage and consequently the megaloblasts, if present, are smaller and more mature.

In an abstract of a paper presented before the New England Pathological Society, Williams<sup>40</sup> reports on histologic studies of megaloblastic marrow which were made for the purpose of determining the criteria by which the megaloblastic can be distinguished from other reactions of the marrow. The material studied consisted of 10 specimens of sternal marrow obtained in 9 cases of pernicious anemia in relapse. It was concluded that the megaloblastic hyperplasia seen in sections of sternal marrow from patients with a red blood cell count of 2,000,000 per cubic millimeter or less presents the following highly characteristic picture: a pronounced increase in cellularity, the presence of large immature basophilic cells, which are clumped together in islands and sinuous columns forming a lacelike network throughout the marrow, the absence of definite islands of mature and moderately mature erythropoiesis, the occurrence of frequent foci of granulopoiesis composed almost exclusively of mature neutrophilic myelocytes, metamyelocytes and polymorphonuclear leukocytes, a striking decrease in the number of megakaryocytes.

It is believed by Limarzi and Levinson<sup>41</sup> that the amitotic and multipolar erythropoiesis which they observed in aspirated specimens of marrow from a patient dying of a rare condition may explain the rapid conversion of megaloblastic to normoblastic marrow following the administration of liver extract to patients with pernicious anemia. They also conclude that evidence is available to support the belief that two different types of erythropoiesis occur simultaneously in the bone marrow of patients with pernicious anemia: the normal bipolar type of mitosis and maturation, and the abnormal form described. They consider that liver therapy acts on the pathologic tissue and possibly results in multipolar mitosis and the development of multinucleated erythroid cells. This, they believe, may explain in part the rapid conversion (not maturation) of megaloblastic to normoblastic marrow within twenty-four hours in some patients with pernicious anemia.

*Changes in the Nervous System in Pernicious Anemia*—The possibility that further light might be thrown on the cause and the nature of subacute combined degeneration of the spinal cord in man by a study of a primary degenerative demyelinating lesion of the spinal cord of the monkey is considered by Hamerton.<sup>42</sup> He studied such lesions as they occurred spontaneously in monkeys of the London Zoo over a period of seven years. Macrocytic anemia was observed in 1 animal, and lymphatic leukemia in another. Achlorhydria was present in the 3 animals studied by gastric analysis. All the monkeys with these lesions showed intention

40 Williams, R. J. The Histology of the Megaloblastic Hyperplasia of the Bone Marrow, *New England J. Med.* **227** 938, 1942.

41 Limarzi, L. R., and Levinson, S. A. Undescribed Type of Erythropoiesis Observed in Human Sternal Marrow and Its Relationship to the Mechanism of Megaloblast-Normoblast Maturation, *Proc. Inst. Med. Chicago* **14** 232, 1942.

42 Hamerton, A. E. Primary Degeneration of the Spinal Cord in Monkeys. A Study in Comparative Pathology, *Brain* **65** 193, 1942.

Sturgis<sup>49</sup> This substance, like thiamine, is alkali labile and hence might be destroyed in the intestinal tract of patients with achlorhydria, so that a deficiency would be caused. In a study of 7 patients with pernicious anemia and a like number of healthy controls it was found that the daily excretion of the substance when determined by the method of Snell, Pennington and Williams<sup>50</sup> both before and after the administration of 100 mg of its calcium salt was slightly but probably not significantly less than that of healthy persons studied in the same manner. This indicates that there is no impairment of its absorption in patients with pernicious anemia. Phillips and Engel<sup>51</sup> report the occurrence of a disease of the spinal cord in chicks receiving a diet deficient in pantothenic acid. The possibility cannot be excluded that the absence of hydrochloric acid may make the riboflavin and the pantothenic acid in food less available for absorption, and therefore the degenerative changes of the nervous system in patients with pernicious anemia may result from a conditioned avitaminosis present over a long period.

*Pernicious Anemia and Carcinoma of the Stomach*—Bronstein<sup>52</sup> adds another to the group of cases of pernicious anemia in which after a variable number of years carcinoma of the stomach has developed. There is certainly no incompatibility between the two diseases. In fact, the question has been asked, Does not the atrophic gastritis of pernicious anemia predispose to the rise of a neoplasm in the gastric mucosa? His patient was a Greek of 45 years who had all of the classic manifestations of true Addisonian pernicious anemia, which responded satisfactorily to parenteral injection of liver extract. After four and one-half years his weight decreased from 127 to 112 pounds (57.5 to 51 Kg). This led to a roentgen examination of the gastrointestinal tract, which disclosed a neoplasm of the middle portion of the stomach, on the side of the greater curvature. At necropsy a fungating tumor (adenocarcinoma) was found involving the fundus of the stomach. At the time the cancer developed, there was a change in the character of the blood picture, as was to be expected. The color index became less than 1.0, the size of the erythrocytes decreased, as did the mean corpuscular hemoglobin concentration. The author discusses the association of pernicious anemia and carcinoma of the stomach and suggests that patients with the former disease should be studied with great care if there is a change in the character of the anemia. The reviewers consider that it is logical to observe an increasing number of patients with the two diseases since, with the modern treatment, those having pernicious anemia now survive to an age when cancer is common. The question is not yet answered as to whether carcinoma of the stomach is more likely to develop in patients with pernicious anemia than in other persons of the same age group, but this is a possibility.

Doehring and Eusterman<sup>53</sup> review the literature dealing with the association of pernicious anemia and carcinoma of the stomach in the same patient, and add a group of cases in which this has been observed at the Mayo Clinic. During the period between 1935 and 1939 approximately 1,014 patients with pernicious

49 Meyer, C. E., Burton, I. F., and Sturgis, C. C. Pantothenic Acid Absorption in Pernicious Anemia, *Proc Soc Exper Biol & Med* **49** 363, 1942.

50 Snell, E. E., Pennington, D., and Williams, R. J. Effect of Diet on Pantothenic Acid Content of Chick Tissues, *J Biol Chem* **133** 559, 1940.

51 Phillips, P. H., and Engel, R. W. Some Histopathologic Observations on Chicks Deficient in Chick Antidermatitis Factor or Pantothenic Acid, *J Nutrition* **18** 227, 1939.

52 Bronstein, L. H. Carcinoma of the Stomach Developing in Pernicious Anemia, *J Lab & Clin Med* **28** 44, 1942.

53 Doehring, P. C., and Eusterman, G. B. Association of Pernicious Anemia and Carcinoma of the Stomach, *Arch Surg* **45** 554 (Oct) 1942.



more than one person of the same family. The mother and a maternal uncle of their patient both had pernicious anemia with subacute combined degeneration of the spinal cord. The data, which the authors admit are "scanty," suggest the transmission of the disease as a mendelian recessive character.

Bleecker<sup>44</sup> reports the case of a patient with a severe involvement of the central nervous system characteristic of subacute combined degeneration of the spinal cord but with a normal blood count, and emphasizes that patients of this type can be benefited with appropriate liver therapy. He states that severe neurologic manifestations do not mean necessarily that permanent damage has been done to the cells of the spinal cord and that function may not return to normal with the proper therapy. He suggests treatment with liver extract in large doses, supplemented by the "gastric factor" (desiccated hog stomach in the case reported), dilute hydrochloric acid, adequate diet and thiamine hydrochloride. He believes that a decrease in the mean corpuscular volume and the mean corpuscular hemoglobin concentration is of favorable prognostic significance.

In relation to subacute combined degeneration of the spinal cord it is possibly of interest that degeneration of sensory neurons involving the peripheral nerves, the posterior root ganglions, the posterior roots and the posterior funiculi of the spinal cord can be produced in pigs by means of a diet deficient in calcium pantothenate or pyridoxine. It is concluded by Wintrobe and his associates<sup>45</sup> that pyridoxine and pantothenic acid are necessary in maintaining the integrity of the nervous system. These neural changes developed in animals when the diets contained adequate amounts of thiamine, riboflavin, nicotinic acid, wheat germ oil and cod liver oil, as well as sufficient protein, carbohydrate, fat and minerals. We are of the opinion that a deficiency of pyridoxine or of pantothenic acid or a disturbance in their metabolism, may account for the lesions of subacute combined degeneration but that the possibility is still a matter for investigation.

It is considered by Meyer, Burton and Sturgis<sup>46</sup> that neural changes in pernicious anemia arise from a deficiency of some unidentified factor other than that required for hemopoiesis. Since achlorhydria is invariably present in patients with pernicious anemia, the possibility must be considered that this condition results from decreased absorption of certain vitamins. Following the report of Street, Cowgill and Zimmerman<sup>47</sup> that a deficiency of riboflavin caused degenerative changes in the peripheral nerves and in the posterior columns of the spinal cord in dogs, Meyer and his associates attempted to determine whether patients with pernicious anemia had diminished ability to absorb riboflavin by measuring the daily urinary excretion according to the method of Snell and Strong<sup>48</sup>. The subjects of the study were 12 hospital patients with pernicious anemia and 12 healthy students, both groups on unrestricted diets, and no indication was found that achlorhydria impaired the absorption of this vitamin. When 5 Gm of riboflavin was added to the diet of each group, no tendency toward a lesser excretion of this substance was observed in the patients with pernicious anemia. These results resemble those obtained in a similar study of the excretion of pantothenic acid reported by Meyer, Burton and

44 Bleecker, P. B. Preanemic Subacute Combined Degeneration of the Spinal Cord. A Case Report, *Mississippi Doctor* **20** 83, 1942.

45 Wintrobe, M. M., and others. Sensory Neuron Degeneration in Pigs. Protection Afforded by Calcium Pantothenate and Pyridoxine, *J. Nutrition* **24** 345, 1942.

46 Meyer, C. E., Burton, I. F., and Sturgis, C. C. Riboflavin Absorption in Pernicious Anemia, *Proc. Soc. Exper. Biol. & Med.* **50** 251, 1942.

47 Street, H. R., Cowgill, G. R., and Zimmerman, H. M. Further Observations of Riboflavin Deficiency in Dog, *J. Nutrition* **22** 7, 1941.

48 Snell, E. E., and Strong, F. M. The Microbiological Assay of Riboflavin, *Indust. & Engin. Chem. (Anal. Ed.)* **11** 346, 1939.

sequent roentgen examinations, the absence of tubercle bacilli in the sputum and the stomach washings and the subsequent favorable course

In a study of 20 patients with pernicious anemia whose hematocrit readings on erythrocytes varied from 11 to 35 per cent, Warner and Owen<sup>57</sup> found the prothrombin level to be between 40 and 65 per cent of normal in a majority of the patients, according to the two stage method of Warner, Binkhous and Smith. When vitamin K was administered in the form of synkamin (4-amino-2-methyl-1-naphthol hydrochloride) either orally or intravenously, no significant change followed. There was a loose correlation between the severity of the anemia and the degree of the hypoprothrombinemia, as there was some tendency for the lowest values to occur in the cases in which the anemia was most severe. No correlation was demonstrable between the degree of hypoprothrombinemia and the amount of damage of the nervous system. The lowest prothrombin level observed in these cases was 40 per cent of normal, which is above the level at which bleeding ordinarily occurs, and there was no evidence of a hemorrhagic tendency. The author states that the clotting power of the blood as measured by the one stage method of Quick or the "bedside" method of Ziffren, Owen, Hoffman and Smith was found to be within normal limits and was not modified by therapy. The interpretation of the failure of the one stage and two stage methods to agree in certain conditions is not known. The beneficial effect of liver extract is possibly attributable to an improvement of the function of the liver. Some evidence is at hand which suggests a mild hepatic insufficiency in cases of pernicious anemia. It is of interest to note that the beneficial effect of liver extract on the production of prothrombin is limited to cases of pernicious anemia, the hypoprothrombinemia observed in newborn infants, in patients with Laennec's cirrhosis, in those with obstructive jaundice and in debilitated patients does not respond to this form of therapy.

An interesting series of comparisons has been made by Strauss and Burchenal<sup>58</sup> of the red blood cell counts and hemoglobin determinations on the capillary and the venous blood of patients with pernicious anemia whose disease was in therapeutically induced remission. The results of a total of 2,139 blood examinations when analyzed revealed that the mean capillary red blood cell count of 80 patients was 4,690,000 per cubic millimeter and the mean venous red blood cell count 4,444,000 per cubic millimeter, a difference of 246,000 per cubic millimeter. This value they consider to be statistically significant, as there is less than 1 chance in 1,000 of its being accidental. The mean of the hemoglobin determinations on the capillary blood of the 80 patients was 91.8 per cent (15.6 Gm per hundred cubic centimeters equals 100 per cent), whereas the mean of the hemoglobin determinations on the venous blood of these patients was 87.3 per cent. They consider that the difference of 4.5 per cent is likewise significant as here also there is less than 1 chance in 1,000 that it is accidental. They conclude, therefore, that the venous blood of patients with pernicious anemia under treatment has approximately 5 per cent less erythrocytes and hemoglobin than the blood obtained from the capillaries. According to the observations reported by Wintrobe and Miller in 1929, the hemoglobin value and the red blood cell count for adult man are the same whether the blood is obtained from the ear or the finger or a vein without stasis. Strauss and Burchenal apparently are not convinced that this is

57 Warner, E. D., and Owen, C. A. Hypoprothrombinemia in Pernicious Anemia. *Am J M Sc* **203** 187, 1942.

58 Strauss, M. B., and Burchenal, J. H. Comparison of Capillary and Venous Red Blood Cell Counts and Hemoglobin Determinations in Patients with Pernicious Anemia in Remission Under Treatment. *J Lab & Clin Med* **27** 937 1942.

anemia were observed at this clinic, and 17 had carcinoma of the stomach, which gives an incidence of 17 per cent. They state that the number of patients in whom these diseases are combined is increasing but that it is difficult to say whether this is due to the increased length of life of patients with pernicious anemia or to some change in the stomach peculiar to Addisonian anemia which makes these patients more likely to have new growths of that organ. It is their opinion that lengthened period of survival accounts in part for the situation. On the other hand, from their calculations they estimate that the incidence of carcinoma of the stomach in patients with pernicious anemia at the clinic is greater than the frequency which one would expect in the same age group in the population at large. In 10 of the 17 cases in which pathologic material was obtained the neoplasm was found to be adenocarcinoma with a varying degree of malignancy. They also observed among 1,014 patients with pernicious anemia 4 with benign polyps, which gives an incidence of 0.39 per cent. The symptoms of pernicious anemia appeared in this group of 17 patients at the average age of 54.5 years, and those of carcinoma of the stomach at 63.2 years. The authors speculate concerning the etiologic relation between the two diseases and conclude that, although the evidence is incomplete, there are grounds for suspecting that persons with pernicious anemia are slightly more likely than other persons to have gastric carcinoma. They also report concerning the relation of anemia to gastric resection that in a series of 474 cases of gastric resection for cancer in 14 of which the operation was total gastrectomy, pernicious anemia developed in not 1 case.

*Miscellaneous Observations Concerning Pernicious Anemia*—In 1937 Snapper, Groen, Hunter and Witts<sup>54</sup> reported a series of cases in which pituitary disease was associated with achlorhydria and anemia, usually of the Addisonian type. Witts<sup>55</sup> now reports 2 more cases, and from what he has learned of others from colleagues he is convinced that the occurrence of these two diseases in the same patient is more than a coincidence. In his opinion, the association of pernicious anemia with hyperthyroidism, with pregnancy and with pituitary disease suggests that there is a defect in some hormonal element or mechanism which may lead to degeneration of the cells in the stomach responsible for the secretion of the intrinsic factor. In his opinion, the combination of this type of anemia with pituitary disease is another example of the precocious senile changes to which the patient with such disease is liable.

The case of a 41 year old white woman with pernicious anemia and lesions reported on roentgen examination of the chest as bilateral pulmonary tuberculosis of undetermined activity is reported by Skavlem and Storey<sup>56</sup>. The association of this blood disorder with pulmonary lesions that possibly were tuberculous caused them to review the literature dealing with the occurrence of these two conditions in the same patient. From the literature they conclude that most writers on this subject agree that the two diseases are rarely seen concurrently and some observers believe that there is antagonism between them. They state that only two authors hold a contrary view, one on grounds not wholly tenable. Their own patient was apparently not suffering from active tuberculosis, as indicated by sub-

54 Snapper, I, Groen, J, Hunter, D, and Witts, L. J. Achlorhydria, Anaemia and Subacute Combined Degeneration in Pituitary and Gonadal Insufficiency, *Quart J Med* 6 195, 1937.

55 Witts, L. J. Pernicious Anaemia and Pituitary Insufficiency, *Lancet* 2 307, 1942.

56 Skavlem, J. H., and Storey, C. H. Concurrent Tuberculosis and Pernicious Anemia, *Ohio State M J* 38 142, 1942.

megaloblastic and those with normoblastic marrow. He believes that diffuse megaloblastic hyperplasia is indicative of deficiency of or of poor utilization of the erythrocyte-maturing factor and that it is an indication for use of liver extract. According to the author, the present day concept of Addisonian anemia includes atrophic gastritis and achylia, which is often associated with glossitis, a constitutional (familial) factor, the resultant lack of intrinsic factor, a continued need of and response to liver therapy. It is considered that the appearance of the anemia may be hastened or precipitated by such factors as deficient intake of animal protein, loss of teeth or change in economic status. This implies that the intrinsic-extrinsic factor relationship obeys the laws of mass action, which in the author's opinion is correct. "Achloric" anemia due to defective utilization of the erythrocyte-maturing factor, as described by Wilkinson, is apparently accepted by Watson with reluctance, as he says he hopes to "deemphasize" it. We agree that it must be an exceedingly rare syndrome in this country. The macrocytic anemias with normoblastic marrow include those of the hemolytic type, both primary and secondary, and those without increased hemolysis. He emphasizes that from the standpoint of therapy the macrocytic anemias should be considered as normochromic or hypochromic. Iron therapy is indicated in the latter, and liver extract, in both groups if the marrow is megaloblastic.

Ten patients with severe degrees of macrocytic anemia and with free acid present in the gastric secretions were studied at the nutrition clinic of the Hillman Hospital by Moore and his associates<sup>63</sup>. All but 1 of the patients showed or had shown the clinical manifestations of pellagra. In 2 patients there was the clinical picture of nontropical spina, 1 patient had a beef tapeworm, and 5 patients were relieved of their diarrhea when nicotinic acid was given. In each patient there was a pronounced shift in the marrow to the younger red cell elements, with a striking increase in megaloblasts. In all instances there was a decided dietary deficiency of animal proteins. It was demonstrated that the intrinsic factor was present in the gastric secretions of 3 patients. Six responded submaximally to the administration of 250 Gm of raw beef muscle. After one week of a diet known to be deficient in animal protein and in vitamin B complex, the crystalline members of this complex were given orally and parenterally without effect on the red blood cells, the marrow or the reticulocytes. An 80 per cent alcoholic extract of beef muscle which was "practically protein free" but known to contain the extrinsic factor produced a rise in reticulocytes and a slight increase in red blood cells. A secondary rise was then obtained in several of the cases by daily administration of the same amount of beef muscle extract which had been incubated with 100 cc of normal human gastric juice. After completion of the observations just described daily parenteral administration of 4 to 6 units of liver extract produced in 9 of the 10 patients a significant increase in the reticulocytes and an acceleration of the formation of red blood cells. These important observations were interpreted as indicating (1) that macrocytic hyperchromic anemia without achlorhydria occurs not infrequently in the southern states where pellagra is endemic and (2) that the anemia is produced both by a dietary deficiency of the extrinsic factor and by poor absorption from the intestinal tract.

Heath<sup>64</sup> considers a group of macrocytic anemias which resemble pernicious anemia but stand apart from this disease because they do not respond favorably to liver extract. He includes in this group macrocytic anemia due to carcinoma

63 Moore, R. A., Spies, T. D. and Cooper, Z. K. Pellagra. *Histopathology of Skin in Pellagra*. Arch. Dermat. & Syph. **46**: 100 (July) 1942.

64 Heath, C. W. Refractory Anemias. Bull. New England M. Center **4**: 11 1942.

true, for they state that the difference they observed in patients with pernicious anemia may also hold for normal persons, but their data are insufficient to prove this point.

In a previous study Ørskov found that the red blood cells of patients with pernicious anemia showed altered permeability to dextrose which was corrected by liver therapy. There were two possible explanations. Either the anti-pernicious-anemia factor acted directly on the red blood cells or new red blood cells with normal permeability were formed. To find out which of these explanations was correct, Ørskov<sup>59</sup> carried out experiments in which liver and desiccated hog stomach were fed by mouth to healthy subjects and the permeability of the red blood cells determined. It was found that the permeability was affected in the same manner as in patients with pernicious anemia, and since the maximum effect was attained on the day following feeding, it was concluded that the anti-pernicious-anemia factor acts directly on the permeability of the red blood cells.

Cooke<sup>60</sup> reports the rather unusual case of a woman aged 30 years with pernicious anemia in which the diagnosis was questioned when she was first observed because there was apparently a spontaneous reticulocyte rise of 30 per cent. This with the acute onset and the fact that the patient had experienced previous attacks with jaundice, suggested the diagnosis of hemolytic jaundice. Subsequently all findings indicated beyond the question of a doubt that the patient did have true Addisonian pernicious anemia. This case brings up the interesting point of the extent of the reticulocyte rise in such patients when their disease is in spontaneous remission. Unfortunately, it is not usual to observe patients at this time. The author offers the suggestion that relapses and remissions may be correlated with varying amounts of the intrinsic factor, which in turn may be associated with variations in the intensity of the gastritis. This, of course, raises the fundamental question as to just what is the cause of the diminution of intrinsic factor in the disease or, in other words, what is the real underlying cause of the disorder. The possibility that gastritis may influence the amount of the intrinsic factor cannot be denied. We should like to emphasize also that variations in the amount of the anti-pernicious-anemia factor might be associated with quantitative changes in the extrinsic factor in the diet.

Arneth<sup>61</sup> has written an article which is mainly a plea for the utilization of the simple laboratory means of examining the blood in the diagnosis of pernicious anemia. He finds the changes thus observed reliable, within the reach of every physician, and present even before the characteristic alterations occur in the marrow. Special emphasis is laid on the "shift to the right" in the Arneth count and on the diminution in the total number of polymorphonuclear cells. As pronounced leukopenia is a feature of the disease during relapse, there is diminution in other types of white blood cells, as well as in neutrophils.

*Macrocytic Anemias Related to Pernicious Anemia*—A complete summary of present knowledge of the macrocytic anemias is presented by Watson,<sup>62</sup> in which a discussion of their etiology, classification and treatment is given. In his opinion, such anemias should be separated into two main groups, namely, those with

59 Ørskov, S. L. Untersuchungen über die Wirkung von per os zugeführtem Leberextrakt und Ventrikelschleimhaut auf die Permeabilität der roten Blutkörperchen beim normalen Menschen, *Acta physiol. Scandinav.* **3** 82, 1941.

60 Cooke, W. T. Unusual Reticulocytosis in Untreated Case (Diagnostic Difficulty), *Brit. M. J.* **2** 806, 1941.

61 Arneth, J. Ueber die qualitativen Blutbefunde bei der perniziösen anämischen Reaktion (perniziösen Anämie) München med. Wchnschr. **89** 371, 1942.

62 Watson, C. J. Macrocytic Anemia, *Illinois M. J.* **82** 195, 1942.

Gordon and Japa<sup>67</sup> report 2 cases of unusual interest in which severe macrocytic anemia developed following gastroenterostomy. One patient, aged 52, had been operated on eleven years before, for a duodenal ulcer. The red blood cell count was 1,630,000 per cubic millimeter and the hemoglobin value was 40 per cent. The sternal puncture revealed normal marrow. Liver therapy produced a good result. A second patient, aged 62, had undergone gastroenterostomy twenty-five years before the development of severe macrocytic anemia. He was benefited with liver extract. The red blood cell count was 1,500,000 per cubic millimeter, the hemoglobin value was 55 per cent, aspirated sternal marrow showed an excessive number of erythroblasts. Achlorhydria was present. The authors believe that it is preferable to speak of these patients as showing macrocytic anemia rather than true pernicious anemia. They state that the condition may have arisen from two causes: first, a lack of intrinsic factor, second, an interference with the flow of intestinal contents, which might interfere with the interaction of the intrinsic and extrinsic factors and impair absorption of the erythrocyte-maturing substance. In criticism of this article Brown<sup>68</sup> makes the following pertinent statements: (1) that the first patient may have had macrocytic anemia but that no facts are given to support this, and that the color index is not helpful unless there is an accompanying statement with reference to the hemoglobin standard used, (2) that the response to liver therapy in a case of anemia in which the sternal marrow is "normal" is sufficiently unusual to justify the inclusion of the hematocrit reading of the packed cell volume, from which the volume of the cells could be calculated, (3) that a note on the criteria of the "good results" which followed the liver therapy would also have been of interest. We are in sympathy with the criticisms expressed by Brown in all instances in which insufficient data are presented by which the reader may evaluate the situation for himself rather than accept statements which merely interpret the findings without presenting them in detail.

Samuel<sup>69</sup> reports the case of a patient who had suffered from chronic gastric ulcer for several years and in December 1936 was treated by cholecystectomy. In June 1938 the man was found to have pernicious anemia. He reacted well to liver therapy. In November he had a severe attack of ulcer pain, which was soon followed by recrudescence of the chronic ulcer distress. The author makes the suggestion that possibly "the production of the intrinsic factor may be interfered with by gastric (and, possibly by hepatic) lesions." Detailed blood findings, the results of gastric analysis and other data which might enable one to make a critical evaluation of the author's statements are not presented. Never in our experience has there been an instance of pernicious anemia and peptic ulcer occurring in the same patient. In one condition there is always achlorhydria, perhaps present from birth and in the other there has invariably been free hydrochloric acid in the gastric secretions. It is entirely possible that the patient may have had macrocytic anemia associated with hepatic disease or with some anomaly of the intestinal tract, but it is unlikely that true Addisonian pernicious anemia and peptic ulcer were both present.

The case of a 64 year old man on whom gastroenterostomy was performed after accidental "swallowing of spirits of salts" is reported by Harlem<sup>70</sup>. Four-

67 Gordon, N. S., and Japa, J. Macrocytic Anaemia Following Gastro-Enterostomy, Brit. M. J. 2 769, 1941.

68 Brown, A. Macrocytic Anaemia Following Gastro-Enterostomy. Brit. M. J. 1 127 1942.

69 Samuel, B. Macrocytic Anaemia After Gastro-Enterostomy. Brit. M. J. 1 55 1942.

70 Harlem, I. C. Macrocytic Anaemia After Gastro-Enterostomy, Brit. M. J. 1 739 1942.

osteosclerosis, the "achrestic" anemia of Wilkinson, the macrocytic anemia sometimes associated with cirrhosis of the liver, and agnogenic myeloid metaplasia of the spleen as recently described by Jackson, Parke and Lemon. He also lists the following conditions which may be accompanied by macrocytosis: acute loss of blood, various hemolytic anemias, hemoglobinuria, various anoxemias, acute heart failure occurring terminally, anemia of infection, anemia of nephritis, myelophthisic anemias and various forms of poisoning. An attempt has been made by the author to distinguish between treatable and refractory macrocytic anemias by a study of the diameters of the erythrocytes. This differential point was suggested by the observation that anisocytosis is usually greater in true pernicious anemia than in certain refractory macrocytic anemias. In this study only cases of macrocytic anemia in which the mean corpuscular volume was 100 cubic microns or greater were utilized. By measuring the diameters of the red blood cells according to the technic of Price-Jones, it was found that below the level of 2,000,000 red blood cells per cubic millimeter the standard deviation of the diameters is helpful in distinguishing pernicious anemia from other macrocytic anemias. The critical level of standard deviation is about 0.9 cubic micron. The deviation is above this level in most cases of pernicious anemia and below it in most cases of severe refractory macrocytic anemia. A second point is helpful in studying the Price-Jones curves. On inspection these curves are not symmetric but are skewed to the right or to the left. It was found that in most cases of pernicious anemia the curve was skewed to the left, whereas in cases of refractory macrocytic anemia the curve is either not skewed or is skewed to the right.

Limarzi<sup>65</sup> reviews the recent advances in the diagnosis and treatment of abnormal conditions of the blood and classifies all cases of anemia into four groups as follows: (1) macrocytic anemia in which the mean corpuscular volume is greater than 94 cubic microns and the mean corpuscular hemoglobin concentration is approximately 30 per cent, (2) normocytic anemia in which the mean corpuscular volume is between 80 and 94 cubic microns and the mean corpuscular hemoglobin concentration is 30 per cent or greater, (3) simple microcytic anemia in which the mean corpuscular volume is less than 80 cubic microns and the mean corpuscular hemoglobin concentration is 30 per cent or higher, (4) hypochromic microcytic anemia in which the mean corpuscular hemoglobin concentration is 29 per cent or less and the mean corpuscular volume is greatly or little reduced or even actually normal. The following diseases are included in the four groups: pernicious anemia, cirrhosis of the liver, sprue, pregnancy, fish tapeworm disease, aplastic anemia, acute leukemias, pellagra, hypothyroidism, carcinoma of the stomach, metastatic lesions of the marrow, lymphoblastomas, agranulocytosis, nephritis, celiac disease, sickle cell anemia, Cooley's anemia and erythroblastosis. Doubtless the author means to indicate that some of these conditions are always associated with macrocytic anemia whereas others may cause macrocytic anemia at times. The article gives a resume of current knowledge concerning the various types of macrocytic anemia with special reference to pernicious anemia.

Berghausen<sup>66</sup> emphasizes that macrocytic anemia may result from a number of causes and that a careful diagnostic study should be made before intensive therapy is initiated. He reports and discusses 5 cases of severe anemia.

<sup>65</sup> Limarzi, L. R. Recent Advances in the Diagnosis and Treatment of Abnormal Blood Conditions, Illinois M. J. **81** 296, 1942.

<sup>66</sup> Berghausen, O. Macrocytic Anemia. Case Reports, Cincinnati J. Med. **22** 547, 1942.

constant finding in pellagra in pernicious anemia and, to a less extent, in sprue. Atrophy of the stomach and intestines may be found in all three diseases. When changes are present in the spinal cord in any of these diseases, the lateral and posterior columns are involved. A review is given of reported cases in which two or all three of these disorders occurred in the same patient. According to them this coincidence suggests common etiologic factors.

Hawes,<sup>74</sup> in an article on sprue and allied disorders, regards several conditions of unknown cause affecting fat metabolism as one entity. In this group he includes celiac disease, idiopathic steatorrhea, nontropical sprue and tropical sprue. According to him, in most cases of steatorrhea anemia is prominent and may assume an erythroblastic, aplastic, hypochromic or a macrocytic, hyperchromic picture. In some cases steatorrhea is indistinguishable from pernicious anemia and in others the blood picture may change from hypochromic to hyperchromic or from macrocytic hyperchromic to hypochromic. The cause of these changes is unknown, but the tendency is for the hypochromic variety to become macrocytic and hyperchromic as the disease advances, especially if the diarrhea persists. Under treatment with liver or liver extract, hyperchromic macrocytic anemia often changes to hypochromic anemia and if then large doses of iron are given, the blood picture returns to normal.

Anemia occurs in virtually all cases of untreated sprue, according to Shookhoff.<sup>75</sup> The macrocytic anemia of the disease may be divided into three types, as follows: (1) that responding to orally administered extrinsic factor, (2) that not responding on the oral administration of this factor but yielding to orally administered liver extract, (3) that responding only on parenteral therapy. It is inferred, therefore, that the macrocytic anemia of sprue may be due to deficiency of the extrinsic factor, reduction in the intrinsic factor, failure of adequate absorption of the hemopoietic principle or a combination of two or all of these mechanisms. Furthermore, some patients with sprue have hypochromic anemia, but the author does not know whether this is to be attributed to inadequacy of the intake of iron or to impairment of the absorption of this element.

Abrahams<sup>76</sup> reports the case of a young woman, 19 years old, with idiopathic steatorrhea, severe macrocytic anemia and glossitis. The red blood cell count was 2,140,000 per cubic millimeter and the hemoglobin content, 20 per cent. The color index was 1.2, and the average diameter of the red cells was 7.9 microns. Recovery followed the administration of a low fat diet, autolyzed yeast (marmite), pills of ferrous carbonate (Blaud's pills), calcium lactate, vitamins A and D and transfusions of blood.

*Assay of Antianemic Materials on Animals*—The study of Stasnev and Burns<sup>77</sup> is another attempt to obtain a method of bioassay for the anti-pernicious-anemia factor, other than the utilization of untreated patients with the disease. They have employed the marsupial opossum because, after an intrauterine life of about twelve days, the immature offspring live in the maternal pouch for an additional ninety days and hence are accessible for the direct injection of anti-pernicious-anemia substance. The fundamental basis for the study is that the

74 Hawes, R. B. Sprue and Allied Disorders, *Practitioner* **149** 157, 1942.

75 Shookhoff, H. B. The Blood Picture in Sprue, *Rev. Gastroenterol.* **9** 338, 1942.

76 Abrahams, A. Idiopathic Steatorrhea with Severe Anemia and Pyrexia, *Proc. Roy. Soc. Med.* **35** 11, 1941.

77 Stasnev, J., and Burns, E. L. Influence of Active and Inactive Antianemic Principles upon Erythrocytes of Immature Opossum (*Didelphys Virginiana*), *Am. J. M. Sc.* **203** 191, 1942.



teen years later evidence of pernicious anemia developed with a hemoglobin value of 60 per cent. The number of red blood cells per cubic millimeter was not determined but measurements demonstrated that the anemia was macrocytic in type for the average diameter of the cells was 8.5 microns. There was a satisfactory clinical response to intramuscular injections of liver extract. The title, "Macrocytic Anaemia After Gastro-Enterostomy," implies a causal relation between the surgical operation and the anemia, although a period of fifteen years intervened. This assumption appears unwarranted, first, because of the long interval and second, because of the scarcity of examples of such a relation in the large number of cases in which gastroenterostomy has been performed in the past few decades.

It is stated by Wayburn<sup>71</sup> that there is a lack of agreement in the literature concerning the incidence of macrocytosis in hepatic disease. In regard to Laennec's cirrhosis alone, for example the more recent figures vary from 41 to 90 per cent. This difference of opinion is attributed in part to the difference in criteria and in classification of the condition involved, and in part to the difference in methods employed in determining macrocytosis. According to the author, the use of determinations of volume is superior, as the lesser degrees of enlargement of cells are detected most readily by volumetric measurements. Ten of 11 patients with acute hepatitis and 12 of 16 with Laennec's cirrhosis had macrocytosis. Of the total of 27 patients, 82 per cent showed macrocytosis. Anemia, if present was slight the lowest hemoglobin content being 74 per cent (12.5 Gm.). The macrocytosis frequently persisted despite treatment, return of the blood count to normal and disappearance of all symptoms. According to the author, the explanation of the macrocytic anemia on the basis of simple failure to store hemopoietic substance in the diseased liver seems inadequate. He suggests that the phenomenon results partly from deficiency of the extrinsic factor and partly from inability of the liver to synthesize the maturation factor.

The case of an Australian soldier in whom macrocytic anemia developed in association with splenomegaly and a prolonged febrile illness due to infective hepatitis is reported by Bonnin.<sup>72</sup> This patient was one of a number who suffered from the disease but was the only one noted to have macrocytic anemia. About five weeks after the onset the hemoglobin value was 70 per cent (Sahli), the red blood cell count 2,200,000 per cubic millimeter and the color index 1.6. The intramuscular injection of various types of liver extract was followed by a typical reticulocyte response and a return of the blood to normal. Eventually the patient made a complete recovery. The anemia was considered to be due to deficiency of the anti-pernicious-anemia factor associated with extensive damage of the liver possibly complicated with excessive destruction of blood.

A comprehensive survey is made by Harris and Harris<sup>73</sup> of the genesis of pellagra, pernicious anemia and sprue. It is their belief that these three conditions are not different manifestations of the same disease but three separate entities. It is conceded, however, that the three appear to be allied nutritional disorders. It is also stated that if the dermatologic manifestations of pellagra are absent, this disease, sprue and pernicious anemia as manifested in oral and gastrointestinal symptoms are indistinguishable from one another. The authors maintain that pathologic change of the liver, usually fatty degeneration is an almost

71 Wayburn, E. Macrocytic Anemia in Liver Disease, *California & West Med* 56 130, 1942.

72 Bonnin, J. M. Macrocytic Anaemia Occurring in Case of Infective Hepatitis, *M. J. Australia* 1 637, 1942.

73 Harris, S., and Harris, S., Jr. The Genesis of Pellagra, Pernicious Anemia and Sprue, *Am. J. Digest. Dis.* 9 29, 1942.

Pace and Fisher<sup>80</sup> attempted to correlate the U S P unitage of liver extract with the method of assay for this material devised by Overbeek, Gaillard, deJongh and Yam. This method depends on measurement of the migration of cells from isolated living guinea pig marrow, embedded in a coagulum of plasma, to which various concentrations of liver extract have been added. At certain optimal concentrations of liver extract the migration is increased and the concentration thus effective is taken as an index of the potency of the liver extract. From the results obtained, a curve was constructed which shows the relation between the dilutions of liver concentrates at which maximal migration of cells from the marrow occurred and the U S P potency of these concentrates. They are of the opinion that this curve may be utilized for the determination of the expected clinical potency of an unknown liver extract.

#### HYPOCHROMIC ANEMIA

*Incidence in Adults and Children*—Restrictions of diet imposed by the exigencies of wartime have raised the question, particularly in England, of the incidence of anemia attributable to iron deficiency. A survey of the hemoglobin values of 1,074 women and children, residents of London and English rural areas, was conducted by Mackay, Dobbs, Wills and Bingham<sup>81</sup>. The age range of the children was 6 months to 18 years. The women included housewives, hospital nurses, medical students and factory workers. The findings of Mackay and her associates when compared with the results of surveys made prior to the war indicated a decrease in hemoglobin presumably attributable to wartime diets, deficient in protein and iron. The differences were not great but appeared to be significant. The incidence of hypochromic anemia was greater among women and children living in the country than in residents of London. In a similar study Davidson and others<sup>82</sup> determined the hemoglobin levels of 831 infants, preschool children and school children of working class families living in Edinburgh, Scotland. The same type of investigation had been carried out in Edinburgh before the war. The authors found that after three years of wartime restrictions no change in hemoglobin levels had occurred in infants but that a decline was observable in older children. They conclude that during peacetime the chief factor influencing nutrition is the economic status of the family, but that in wartime food rationing and the difficulties of obtaining unrationed foods are the most important factors, irrespective of income.

The hemoglobin values of school children in Southern Rhodesia, South Africa, were determined by Jones<sup>83</sup>. The Newcomer method was employed, and a range of 120 to 149 Gm of hemoglobin per hundred cubic centimeters of blood was adopted as normal. On this basis, the incidence of anemia among 2,173 European children was 14.7 per cent, and that among 304 Negro children was 23 per cent. The predominant factors causing anemia were considered to be faulty diet and parasitic infection. Morales<sup>84</sup> examined the blood of 104 Puerto Rican girls

80 Pace, N., and Fisher, R. S. Assay of Anti-Pernicious Anemia Liver Concentrates by the Use of an Isolated Bone Marrow Preparation, *J. Pharmacol. & Exper. Therap.* **74**: 256, 1942.

81 Mackay, H. M. M., Dobbs, R. H., Wills, L., and Bingham, K. Anaemia in Women and Children on War-Time Diets, *Lancet* **2**: 32, 1942.

82 Davidson, L. S. P., and others. Nutritional Iron Deficiency Anaemia in Wartime. The Haemoglobin Levels of Eight Hundred and Thirty-One Infants and Children, *Brit. M. J.* **2**: 505, 1942.

83 Jones, E. B. Sub-Clinical Anaemia of School-Children in Southern Rhodesia, *Tr. Roy. Soc. Trop. Med. & Hyg.* **36**: 99, 1942.

84 Morales, F. H. Blood Studies in Puerto Rican Children, *Puerto Rico J. Pub. Health & Trop. Med.* **17**: 387, 1942.

erythrocytes of patients with pernicious anemia and those of mammalian fetuses are similar in some respects, so that the activity of the anti-pernicious-anemia substance might be measured by an acceleration of the rate of maturation of the fetal erythrocytes. Extensive observations showed that the immature developing opossum, living in the maternal pouch, did have macrocytic anemia, which disappeared in adult life. The direct injection of either concentrated normal human gastric juice or liver extract reduced the mean "maximal diameter and the mean corpuscular volume significantly and increased the number of erythrocytes. On the other hand, these changes did not follow the injection of inactivated normal human gastric juice or liver extract or the gastric juice from a patient with Addisonian pernicious anemia. These results seem promising, but reference should be made to the study of Last and Hays<sup>78</sup> in which confirmatory results were not obtained. The latter emphasize as others have done the great desirability of a readily available method of assay for the anti-pernicious-anemia factor and turn to a study of the effect of the principle on the maturation of embryonic blood cells as a possible help in this direction. They emphasize that the primitive generation of erythrocytes in the embryo, though morphologically similar to the megaloblastic generation of pernicious anemia is not identical with it. The possibility, however, that embryonic megaloblastic and erythroblastic erythropoiesis might respond similarly to liver therapy has stimulated interest in the fetal approach to the bioassay problem. Their own studies have been an attempt to confirm the positive findings in the young of the opossum pouch and 11 day rat fetuses. Contrary to other reports, however, no accelerated maturation of the erythrocytes as reflected by a significant decrease of the mean corpuscular volume was observed in the pouch young receiving liver therapy nor were positive results obtained when 15 and 20 day rat fetuses were employed. They conclude that the embryogenesis of blood in the opossum and the rat is unaffected by the anti-pernicious-anemia principle and that neither embryo should be utilized in the bioassay of anti-pernicious-anemia preparations. In discussing the negative results obtained in the fetal approach to the bioassay problem the authors point out a fallacy in its rationale namely that the immature cell of the premature embryonic and that of the megaloblastic generation are not cytologically identical and that, furthermore, the macrocytes in the blood of patients with pernicious anemia reflect a megaloblastic erythropoiesis which is an abnormal phenomenon, whereas the large erythrocytes in embryonic blood are the mature elements of a primitive system of erythropoiesis which is a normal physiologic process. We consider that, allowing as the fetal method of bioassay may seem when first considered, the objections cited appear to be valid.

An article by Hays, Last and Koch<sup>79</sup> summarizes their observations of the effect of liver extract on erythropoiesis in the chick embryo. It is advantageous to use the chick embryo as the liver fraction can be injected directly into it without depending on placental transfer and, in addition, the absolute age is known with certainty. They conclude, however, after careful studies, that the rate of erythropoiesis in the 3 to 7 day old chick embryo cannot be utilized as a specific means of assay for liver extract, as the changes observed are not statistically significant.

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78 Last, J. H., and Hays, E. E. The Action of the Antipernicious Anemia Principle on the Blood Picture of Opossum Pouch-Young and Rat Embryos, *Am J M Sc* **203** 836, 1942.

79 Hays, E. E., Last, J. H., and Koch, F. C. Effect of Liver Extracts upon Erythropoiesis in Chick Embryo, *Am J M Sc* **203** 843, 1942.

value only in the treatment of patients who have been anemic for a short time. Presumably this group includes those with acute loss of blood. In patients whose hypochromic anemia is more chronic, medicinal iron supplemented by the vitamin B complex is of temporary value, regardless of the quality of the diet, but the anemia tends to recur on discontinuance of the medication. He reports that a proprietary preparation containing iron and a liver concentrate which is misleadingly termed "whole liver," provides a beneficial effect which persists after the discontinuance of treatment and "is apparently capable of compensating for shortcomings in the diet." This contribution so contrary to the recorded experience of clinicians generally, would scarcely warrant mention were it not for the widespread publicity which is accorded to such reports through commercial channels. Physicians generally should realize that the only medicinal agent of clinically proved value in the treatment of hypochromic anemia is iron but that in cases in which dietary deficiencies occur therapeutic management should be based on appraisal of the individual nutritional status. Castle<sup>20</sup> states "Iron, therefore, appears to be the only agent of practical importance in the treatment of hypochromic anemia." Hoffman and Kracke<sup>90</sup> state, "Mixed shotgun therapy is entirely unwarranted and it is extremely expensive for the patient." Other recent articles dealing with the treatment of hypochromic anemia and confirming the therapeutic value of unsupplemented iron salts have been published by Fowler,<sup>91</sup> Bethea<sup>92</sup> and Beard<sup>93</sup>.

*Anemia in Pregnancy*—According to Peralta-Ramos and Gascon,<sup>94</sup> Hippocrates observed the pallor of pregnant women and attributed it to the additional drain of the fetus. H. Nase, in 1836, was the first to find evidence of a decrease in the number of erythrocytes during pregnancy, and he attributed it to an increase in plasma volume. Numerous studies by many investigators have upheld the essential truth of these observations. The present authors examined the blood of 1,012 women in Argentina at intervals throughout gestation and arrived at the following conclusions. The majority of healthy pregnant women show a decrease in the concentration of circulating erythrocytes beginning during the first month and reaching a maximum at the ninth month of gestation, the hemoglobin level is also lowered, but the rate of decline becomes slowed during the last trimester. Determinations of the freezing point of the plasma, the concentration of the plasma proteins, the concentration of bilirubin and the number of circulating monocytes lent support to the view of the authors that the oligocythemia occurring during pregnancy is due to a physiologic increase in the destruction of red blood cells rather than to hemodilution. We agree that the evidence indicates increased breakdown of erythrocytes during pregnancy but believe that ordinarily this change is compensated for by more active regeneration of erythrocytes. On the other hand, increased volume of plasma has been demonstrated by numerous quantitative studies and can readily explain the physiologic oligocythemia of pregnancy.

The hemoglobin levels of 392 pregnant women were determined by Hamilton and Wright<sup>95</sup> at intervals from about the third month to the termination of

90 Hoffman, B. J., and Kracke, R. R. The Diagnosis and Treatment of Hypochromic Anemias, *South Med & Surg* **104** 1, 1942.

91 Fowler, W. M. Iron Deficiency Anemias, *Clin Med* **49** 74, 1942.

92 Bethea, J. M. Uses and Misuses of Iron and Liver Extracts in Treatment of Anemias, *Memphis M J* **16** 187, 1941.

93 Beard, M. F. Treatment of Anemia, *Kentucky M J* **40** 161, 1942.

94 Peralta-Ramos, A., and Gascon, A. A proposito de la pseudo-anemia del embarazo, *Prensa med argent* **29** 929, 1942.

95 Hamilton, H. A., and Wright, H. P. Development of Hypochromic Anaemia During Pregnancy. Response to Iron Therapy, *Lancet* **2** 184, 1942.

between the ages of 8 and 18 years. He found subnormal blood values for 82 per cent of these girls. The anemia was macrocytic in 52 per cent and hypochromic in 38 per cent. The diets of these subjects were low in calories, protein and minerals, including iron. No attempt was made to estimate the intake of vitamins.

No relation between the hemoglobin level and the daily intake of vitamin C was found by Thomson, Glazebrook and Millar<sup>85</sup> in a study of adolescent boys living in an institution. The diet of all the subjects was low in vitamin C, but one group was given the vitamin as a medicinal supplement. Apparently, determinations of blood ascorbic acid were not performed.

A case of idiopathic hypochromic anemia occurring in a man is reported by Currie<sup>86</sup>. The patient was 28 years old, his diet was considered to have been average in quality and quantity and he had no evidence of hemorrhage. Achlorhydria was found, the erythrocyte count was 3,700,000 per cubic millimeter and the hemoglobin, 48 per cent. The sternal marrow was normoblastic. A reticulocyte response with increase in blood values followed treatment with iron and ammonium citrates. In a young male this type of blood picture not associated with demonstrable loss of blood is most unusual and always raises the question of occult hemorrhage. We have observed such patients who proved to have intermittent bleeding from intestinal telangiectases. The case of a man 46 years old with severe hypochromic anemia, achlorhydria and koilonychia is reported by Clarke<sup>87</sup>. The patient had bleeding hemorrhoids, his symptoms were attributable entirely to the anemia, his heart was enlarged, his tongue was beefy red and he showed no evidence of neurologic change. Recovery followed administration of iron and ammonium citrates, 4 Gm daily, but the anemia recurred when treatment was taken irregularly. Following a second remission induced by ferrous sulfate, 1 Gm daily, the return of hydrochloric acid in the gastric secretions was observed.

The regeneration of hemoglobin after donations of blood was studied by Fowler and Barer<sup>88</sup>. After an average withdrawal of 555 cc the mean decline of hemoglobin in 200 donors was 2.3 Gm per hundred cubic centimeters. In the majority of instances the predonation level was restored in less than fifty days but 25.8 per cent of the subjects required more than two months for complete recovery. The rate of regeneration was not retarded after multiple donations. It was slower in females than in males. The administration of iron and ammonium citrates, 1 Gm daily, was accompanied by an increase in the average daily regeneration of hemoglobin amounting to 49 per cent and the period of recovery was shortened from an average of forty-nine and six-tenths to one of thirty-five and two-tenths days after the initial withdrawal of blood. Following subsequent donations treatment with iron had progressively less effect on the period of recovery.

In an extraordinary article Gottlieb<sup>89</sup> reports on evaluation of therapy in cases of hypochromic anemia. He draws the conclusion that iron salts alone are of

85 Thomson, S., Glazebrook, A. J., and Millar, W. G. Vitamin C and Anaemia, with Description of Photoelectric Colorimeter, *J. Hyg.* **42**: 103, 1942.

86 Currie, I. P. Idiopathic Hypochromic Anaemia in a Male Adult, *Brit. M. J.* **1**: 762, 1942.

87 Clarke, B. G. Hypochromic Anemia with Koilonychia (Spoon Nails). Report of Case, *New England J. Med.* **227**: 338, 1942.

88 Fowler, W. M. and Barer, A. P. Rate of Hemoglobin Regeneration in Blood Donors, *J. A. M. A.* **118**: 421 (Feb. 7) 1942.

89 Gottlieb, R. Whole Liver as an Adjuvant to Iron in the Treatment of Hypochromic Anaemia, *Canad. M. A. J.* **47**: 456, 1942.

to any form of therapy except transfusion of blood and termination of the pregnancy. The authors report that in pregnancy the microcytic hypochromic type of anemia may develop into the macrocytic type with a high color index during treatment with iron compounds. In the treatment of anemia of pregnancy as observed in India, they found the combined administration of medicinal iron and liver extract to be of greatest value. Thirty of the patients in this series were observed for two to three months after delivery, and all exhibited normal hematologic values. Mudaliar and Menon see a resemblance between the macrocytic anemia of pregnancy and preeclamptic toxemia. In many of their patients diarrhea preceded the severe symptoms of anemia. In some instances ancylostomiasis may have been an etiologic factor.

A case of macrocytic anemia in pregnancy associated with preeclamptic toxemia is reported by Procopie and Armington<sup>101</sup>. The anemia was attributed to defective diet with hyperemesis and disturbance of gastric secretion. Improvement followed administration of liver extract.

The construction of diets to meet the needs of women during pregnancy and lactation is outlined by Bethell and Blecha<sup>102</sup>. In a study of the nutritional and the hematologic status of 495 women residing in rural areas of Michigan a positive correlation was found between dietary deficiency of iron and hypochromic anemia, and between inadequate intake of protein from animal sources and macrocytic anemia.

On the African Gold Coast over a ten year period macrocytic anemia occurred in 100 hospitalized pregnant women, approximating 1 per cent of the total number of such women, according to Russell<sup>103</sup>. Sixty-four of the subjects were primiparas. In 29 of the women the anemia occurred before the twenty-eighth week of gestation. The incidence of malaria, 29 per cent, and that of a positive Wassermann reaction were about the same in the group with anemia as in the population in general. In most of the patients the anemia was severe, but they responded well to liver extract therapy, and spontaneous recovery usually followed termination of the pregnancy. The author reports that discontinuance of liver therapy after remission had been induced was not followed by recurrence of anemia during the same pregnancy but that often the anemia reappeared during subsequent pregnancies. If the macrocytic anemia remains untreated, the prognosis is poor. The mortality of hospitalized patients with macrocytic anemia was 5 per cent. The author believes that the causation of the macrocytic anemia observed on the Gold Coast is complex and varied. The most important factors, in order of probability were dietary deficiency, especially of the "extrinsic factor" of Castle, disturbance of gastric secretion, intercurrent disease, such as malaria, and pre-existing anemia from deficiency of iron.

The case of a 29 year old multipara, born in Ireland, who was first observed just before the termination of pregnancy, is reported by Daniel and Antis<sup>104</sup>. The erythrocyte count was 860,000 per cubic millimeter, the hematocrit reading was 12 per cent and the hemoglobin value 18 per cent. Because of persistent nausea and vomiting, her diet had been greatly restricted since the second month of gestation. Free hydrochloric acid was present in the gastric contents. The patient

101 Procopie, G, and Armington, C. Pregnancy Complicated by Preeclamptic Toxemia and Pernicious Anemia, *J Indiana M A* **35** 466, 1942.

102 Bethell, F H, and Blecha, E. The Diet in Pregnancy, *Clinics* **1** 346, 1942.

103 Russell, B A S. Macrocytic Anaemia in Pregnant Women on Gold Coast, *Lancet* **2** 792, 1941.

104 Daniel, M, and Antis, M. Macrocytic Hyperchromic Anemia of Pregnancy, *Am J Obst & Gynec* **44** 93, 1942.

gestation. Iron and ammonium citrates 6 Gm daily, were administered to one half of the group except for certain ones who received ferrous sulfate. The average hemoglobin level of the untreated subjects showed a decline, whereas that of the treated women was elevated. A comparison with data acquired earlier on a similar class of subjects led the authors to the conclusion that the incidence of anemia among pregnant women of the artisan class was higher than before the war. The change was attributed to nutritional deficiency, and routine prenatal administration of iron as a prophylactic measure as well as improvement of the diet was advocated. A similar conclusion was reached by Thomas<sup>96</sup> as a result of determinations of hemoglobin in cases of pregnancy.

In Coorg, India considered an unhealthy locality, low hemoglobin values among pregnant women and children are exceedingly prevalent, according to Bhavé and Bopaiya.<sup>97</sup> The deficiency is attributed to poor diet and to malarial and hookworm infection, and was remedied by administration of medicinal iron. A monograph of 135 pages on the incidence, the type and the response to therapy of anemia observed in 529 pregnant women in Calcutta, India, has been published by Napier and Neal-Edwards.<sup>98</sup> The data are considered with reference to age, parity, nutritional status, religion and other attributes of the subjects and are too involved and extensive to be reviewed here. This most complete study should, however, serve as a valuable reference.

Sixteen cases of macrocytic anemia occurring in pregnant women are reported and described by Davidson, Davis and Innes.<sup>99</sup> Macrocytosis, anisocytosis and presence of oval erythrocytes were not as prominent in the blood of these patients as in that of patients with true pernicious anemia. Sternal aspiration revealed a megaloblastic reaction of the marrow in all but 1 of the 13 cases in which it was performed. A temporary refractory period followed institution of parenteral liver therapy in 10 of the patients, but eventually all responded. The authors suggest that the transient arrest of erythropoiesis may have been due to the absence of some factor not supplied by liver extract and possibly contained in protein or that the delay in therapeutic response may have been due to inability of the marrow to utilize the hematinic principle of liver as a result of the strain of pregnancy and the shock of labor in a severely anemic woman. A decided drop in the blood values of these subjects was observed after delivery.

One hundred and three cases of macrocytic anemia occurring in pregnant women in India are reported by Mudaliar and Menon.<sup>100</sup> The subjects were of varied economic status and dietary habits. No deficiency of protein or of vitamin B complex was recognized, but the diets generally appeared to be inadequate in vitamins A, C and D. Anemia of macrocytic type was observed more frequently in multiparas than in primiparas and was recognized usually in the second or the third trimester. The color index was more often above than below unity. Contrary to the reported experience of others, the authors found autolyzed yeast (marmite) of no therapeutic value. Crude and refined concentrated liver extracts were equally effective in relieving the anemia, but in some instances there was no response.

96 Thomas, R. C. Haemoglobin of Pregnant Women, *Brit. M. J.* **1** 88, 1942.

97 Bhavé, P. D., and Bopaiya, M. S. Diet Surveys and Investigations of Haemoglobin Levels in Coorg, *Indian J. M. Research* **30** 53, 1942.

98 Napier, L. E., and Neal-Edwards, M. I. Anaemia in Pregnancy in Calcutta: Analysis of Haematological and Other Data from Five Hundred and Twenty-Nine Pregnant Women, *Indian M. Research Mem.*, 1941, no. 33, p. 1.

99 Davidson, L. S. P., Davis, L. J., and Innes, J. Megaloblastic Anaemia of Pregnancy and the Puerperium, *Brit. M. J.* **2** 31, 1942.

100 Mudaliar, A. L., and Menon, M. K. K. The Macrocytic Anaemia of Pregnancy, *J. Obst. & Gynaec. Brit. Emp.* **49** 284, 1942.

value before delivery than to the quantity of blood subsequently lost. The author also states that "the low prenatal blood values prevailing among negroes on this service are an important factor contributing to their much greater incidence of puerperal morbidity."

Evidence concerning the rate of transmission of iron from the maternal alimentary tract to the blood of the human fetus was obtained by Pommerenke and his co-workers<sup>109</sup>. They fed single doses of iron containing the radioactive isotope to pregnant women shortly before delivery or before therapeutic abortion. The radioactive iron was detected in the fetal circulation in as short a time as forty minutes after its ingestion by the mother. The authors therefore conclude that the plasma rather than the erythrocytes, which would have to undergo preliminary disintegration, must be the vehicle for the transmission of iron from the mother to the fetus. In the fetal tissues there was wide dissemination of radioactive iron, with the largest portion present in the erythrocytes and the next largest in the liver.

*Mineral Metabolism and Experimental Anemia*—The phosphorus content of the whole blood and of the erythrocytes of 7 anemic children was determined by Behrendt<sup>110</sup>. In 5 children the anemia was of the hypochromic variety, while in 2 the blood picture was characterized by a color index greater than 1. No correlation was observed between the retention of phosphorus by the red cells and the presence of any kind of pathologic blood cells or any special type of anemia.

In order to determine the effect of a high fat intake on the rate of destruction of erythrocytes as measured by the excretion of urobilin, Josephs and his associates<sup>111</sup> fed 6 normal infants between 5 and 8 months of age on diets which derived from 35 to 85 per cent of their caloric value from fats. They found an increase of the fecal output of urobilin during the period of these diets, an increase independent of the type of fat. Free fatty acids and soaps exerted a similar effect, suggestive of increased hemolysis. There was also an abrupt but temporary rise in the excretion of iron, which suggested to the authors that there may have been either a "washing out" of iron from storage depots or an excessive output of hemoglobin which was later counterbalanced by increased production of hemoglobin. They are of the opinion that the hemolytic action of fats is probably due to the formation and absorption of soaps or fatty acids. In the healthy infants studied the hemolytic effect was insufficient to produce anemia or a rise in reticulocytes, but the authors suggest that when the bone marrow is already being subjected to strain, such a diet may aggravate the situation.

Studies of the iron balance of 66 young women between the ages of 16 and 27 years who were subsisting on self-chosen diets were undertaken by Leverton and Marsh<sup>112</sup>. Observations were carried out during ninety-nine one week periods. The average daily intake of iron provided an average daily storage of 1.37 mg, which was considered ample for replacement of normal menstrual losses. The authors state that diets optimum in other essential foods appear to influence favorably the absorption of iron.

109 Pommerenke, W. T., Hahn, P. F., Bale, W. F., and Balfour, W. M. Transmission of Radioactive Iron to the Human Fetus, *Am J Physiol* **137** 164, 1942.

110 Behrendt, H. Studies on Blood Phosphorus. Intracellular and Extracellular Blood Phosphorus in Anemia in Children and in Experimental Anemia, *Am J Dis Child* **64** 789 (July) 1942.

111 Josephs, H. W., Holt, L. E., Jr., Tidwell, H. C., and Kajdi, C. Influence of Dietary Fat upon Excretion of Urobilin, *Bull Johns Hopkins Hosp* **71** 84, 1942.

112 Leverton, R. M., and Marsh, A. G. The Iron Metabolism and Requirement of Young Women, *J Nutrition* **23** 229, 1942.



responded to transfusion of blood and parenteral injection of liver and was delivered spontaneously of a full term living child

Nineteen cases of severe anemia associated with pregnancy or the puerperium are reported by Leschei<sup>105</sup>. Nine of the women had 'pernicious anemia of pregnancy' and hemolytic anemia of the Lederer type characterized by an abrupt onset. The patients in the former group were chiefly in the middle and later years of the reproductive period, and the condition developed insidiously during the last trimester of gestation. The changes in the quantitative and morphologic characteristics of the blood were similar to those observed in true pernicious anemia but macrocytosis was less marked, and leukopenia was absent. In none of the patients were there signs referable to changes in the central nervous system and in all there occurred a prompt response to liver therapy. In the group characterized by hemolytic anemia, the rapid lowering of the blood values was not associated with spherocytosis or with increased fragility of the erythrocytes. Reticulocytosis and bilirubinemia were present. The anemia failed to respond to liver therapy but the condition was often completely relieved by blood transfusion.

The case of a 27 year old typist who presented the features of aplastic anemia at the fourth month of gestation is reported by Hurwitt and Field<sup>106</sup>. Hemorrhagic manifestations predominated, all of the cellular elements arising from the marrow were reduced in number and at necropsy the diagnosis was confirmed. The authors review the literature on the subject and find evidence that the association of aplastic anemia and pregnancy may be more than coincidental. In such cases they advise termination of the pregnancy whenever this is feasible. Stodtmeister and Buchmann<sup>107</sup> report a case of aplastic anemia in a woman of 41 years who was first seen twelve days after she had given birth to a full term healthy infant. There was a history of progressive weakness and increasing edema throughout the last two months of gestation. The erythrocyte count was said to be 300 000 per cubic millimeter and the hemoglobin value 10 per cent. The leukocyte count was 14,200 per cubic millimeter with a neutrophil percentage of 79. The platelet values were not abnormal. Free acid was present in the gastric contents. No response was observed following parenteral injection of a product corresponding to a purified solution of liver U. S. P., but the patient recovered after blood transfusions. Aspirated sternal marrow revealed a selective absence of maturation of erythrocytic elements. The authors draw an analogy between such inhibition of erythropoiesis leading to "acute aplastic anemia" and a similar arrest of granulocyte or platelet development giving rise, respectively to agranulocytosis and thrombocytopenic purpura.

The hemoglobin levels and the incidence of febrile puerperal morbidity among 1 001 multiparas were correlated by Bickerstaff<sup>108</sup>. He found an almost uninterrupted decline in the incidence of febrile morbidity with increasing values of hemoglobin the relationship persisting until the hemoglobin level approached 12 Gm per hundred cubic centimeters. Excessive loss of blood at parturition was also related to the incidence of fever, but unless the hemorrhage was of a serious degree, the occurrence of fever was more closely related to the hemoglobin

105 Leschei, F. G. Grave Anaemias in Pregnancy and the Puerperium. Report of Seventeen Cases, *Lancet* **2** 148, 1942.

106 Hurwitt, E. S., and Field, L. Aplastic Anemia in Pregnancy, *Am J Obst & Gynec* **43** 42, 1942.

107 Stodtmeister, R. and Buchmann, P. Ueber aplastisch-anämische Krise in der Schwangerschaft, *Klin Wchnschr* **21** 701, 1942.

108 Bickerstaff, H. J. Relationship Between Late Prenatal Hemoglobin Levels and Febrile Puerperal Morbidity, *Am J Obst & Gynec* **43** 997, 1942.

article Hahn and his associates<sup>117a</sup> report that values for the total erythrocyte volumes of normal and anemic dogs when determined either by vivipercfusion<sup>117b</sup> or by the use of "radioactive iron tagged red cells" were from 10 to 40 per cent lower than the values obtained by simultaneous hematocrit and plasma volume determinations. They state that because of the relatively stationary plasma film next to the walls of the vessels the hematocrit value of the entire vascular system is considerably below that of the large vessels and that the cell plasma ratio of the smaller vessels is still lower. In the dog they found no evidence of considerable stores of immobilized red cells. The "rapidly circulating blood volume" obtained by dividing the erythrocyte volume as measured by the radioactive iron method by the venous hematocrit value was found to be considerably less than the total blood volume. The "rapidly circulating blood plasma" amounts to about 80 per cent of the total blood plasma.

A number of other studies dealing with mineral metabolism and factors in the production of hemoglobin in experimental and clinical anemic states have been published by the group in Rochester, N. Y., working under the direction of G. H. Whipple. Balfour and his associates<sup>118</sup> studied the absorption of iron by means of its radioactive isotope in 34 patients with a variety of clinical conditions. The absorption was increased in pregnancy but not in pernicious anemia, hemochromatosis, familial icterus, erythroblastic anemia, leukemia, chronic infections and polycythemia. They believe that the absorption of iron is governed by the reserve stores of iron in the body rather than by the presence of anemia and that "this control is exerted upon the gastro-intestinal mucosa which can refuse or accept iron under various conditions."

Cruz, Hahn and Bale<sup>119</sup> produced acute destruction of red cells by administering acetylphenylhydrazine to non-depleted dogs and to others with adequate or excessive iron stores. Previously, radioactive iron had been introduced into the erythrocytes by oral administration over a twenty-day period. The radioactive iron was detected and measured in the new erythrocytes formed in response to the hemolysis within a few days and as soon as there was evidence of regeneration. This occurred in all the dogs, irrespective of depletion or of excess storage of iron and indicated that the greater part of the iron utilized in the synthesis of hemoglobin is derived directly from disintegrated erythrocytes rather than from storage reserves. According to Cruz, Hawkins and Whipple,<sup>120</sup> healthy, non-anemic dogs in which bile fistulas have been produced excrete hemoglobin pigment almost quantitatively after either the administration of acetylphenylhydrazine or the intravenous injection of hemoglobin, but the animals' capacity to form new hemoglobin remains unimpaired and the regeneration is not affected significantly by the constituents of the diet.

117 (a) Hahn, P. F., and others. Red Cell and Plasma Volumes (Circulating and Total), as Determined by Radio Iron and by Dye, *J. Exper. Med.* **75** 221, 1942. (b) Whipple, G. H. Hemoglobin of Striated Muscle. Variations Due to Age and Exercise, *Am. J. Physiol.* **76** 693, 1926.

118 Balfour, W. M., and others. Radioactive Iron Absorption in Clinical Conditions Normal, Pregnancy, Anemia, and Hemochromatosis, *J. Exper. Med.* **76** 15, 1942.

119 Cruz, W. O., Hahn, P. F., and Bale, W. F. Hemoglobin Radioactive Iron Liberated by Erythrocyte Destruction (Acetyl Phenylhydrazine), Promptly Reutilized to Form New Hemoglobin, *Am. J. Physiol.* **135** 595, 1942.

120 Cruz, W. O., Hawkins, W. B., and Whipple, G. H. Acetyl Phenylhydrazine Anemia, Bile Pigment Elimination and New Hemoglobin Reconstruction in Bile Fistula Dog, *Am. J. M. Sc.* **203** 848, 1942.

Black and Powell<sup>113</sup> gave 1 liter of blood by duodenal tube to each of 2 patients with iron deficiency anemia associated with achlorhydria and to a normal person with abundant secretion of hydrochloric acid. From 10 to 25 per cent of the iron contained in the ingested blood was not recovered in the feces, although a larger amount was excreted by the healthy subject. Of the iron which was apparently absorbed, some but not all could be accounted for as "easily split-off" iron (Baikan). The remainder must have been derived from hemoglobin, which indicates that contrary to earlier reports, in the alimentary tract the hemoglobin molecule may be decomposed with release of an absorbable iron compound, even in the presence of achlorhydria.

The iron and the copper contents of the livers, spleens, stomachs and when present, tumor tissue of 15 control subjects, 23 patients with cancer plus anemia and 11 patients with noncancerous diseases plus correspondingly severe anemia were determined by Gross, Sandberg and Holly.<sup>114</sup> There was abundant storage of iron and copper in the livers and spleens of many patients with cancer, and the level of storage bore no relation to the incidence or the severity of anemia. There were normal or greater than normal amounts of iron and copper in the stomachs of such patients, so that the hypochromic anemia could not be accounted for by inadequate stores of these metals. The tumor tissue itself showed marked affinity for copper.

The hypochromic iron deficiency anemia induced in adult dogs by repeated venesection failed to respond to the administration of iron and copper salts when high levels of cobalt were added to the diet, according to McKibbin and his co-workers.<sup>115</sup> Rapid regeneration of hemoglobin occurred, however, when the ration was further supplemented with dry whole liver or liver extracts. The authors report that synthetic B vitamins, bile salts, cysteine, uropterin concentrates and large doses of iron when fed individually failed to exhibit the activity of liver preparations but that when all of these supplements were administered collectively, regeneration of blood occurred comparable to that induced with liver preparations. However, in animals fed the mixture of pure supplements the blood plasma iron was not mobilized, as it always is during liver therapy. They also found that when dogs with chronic anemia due to withdrawal of blood were fed a highly purified ration supplemented only with synthetic vitamins they retained their ability to regenerate hemoglobin and erythrocytes and that recovery was complete in two weeks after discontinuance of phlebotomy.

The blood volume of the dog is constant, in spite of varying degrees of anemia according to Hahn, Bale and Balfour,<sup>116</sup> whose studies were based on the use of radioactive iron. They found that deficits in erythrocytes were compensated for by corresponding increases in plasma volume and that radioactive iron contained within circulating red cells was reutilized promptly in the formation of new erythrocytes after the physiologic destruction of the older forms. In another

113 Black, D. A. K., and Powell, J. F. Absorption of Haemoglobin Iron, *Biochem J* **36** 110, 1942.

114 Gross, H., Sandberg, M., and Holly, O. M. Changes in Copper and Iron Retention in Chronic Diseases Accompanied by Secondary Anemia. Changes in Liver, Spleen and Stomach, *Am J M Sc* **204** 201, 1942.

115 McKibbin, J. M., Schaefer, A. E., Elvehjem, C. A., and Hart, E. B. Studies on Hemorrhagic Anemia in Dogs, *J Biol Chem* **145** 107, 1942.

116 Hahn, P. F., Bale, W. F., and Balfour, W. M. Radioactive Iron Used to Study Red Blood Cells over Long Periods. The Constancy of the Total Blood Volume in Dogs, *Am J Physiol* **135** 600, 1942.

Iron in the form of chelidamate complexes was administered parenterally to rats and rabbits by Brownlee, Bambridge and Thorp<sup>126</sup> These preparations were shown to be rapidly transported to the liver, the spleen and the kidneys and to be outstanding as factors in the production of hemoglobin by iron-deficient animals After parenteral injection none of the iron was excreted by the intestine They found that injected iron was exceedingly toxic to rats with hypochromic anemia

To rats who had been made severely anemic by means of an exclusive milk diet Freeman and Ivy<sup>127</sup> fed supplements of iron, copper and manganese, and to different groups various antacids were given They found that the retention of iron by these animals was greatly reduced when either calcium carbonate or aluminum hydroxide was given Magnesium trisilicate caused a reduction in retention of iron, but to a degree of questionable significance Aluminum phosphate had no effect on the retention of iron The determinations were made by ashing the animal carcasses entire The conclusion is drawn that the intake of iron should be increased in cases in which there is consumption of aluminum hydroxide or calcium carbonate

Gyorgy<sup>128</sup> and his co-workers found that crude linoleic acid fed with or without butter yellow in a synthetic diet was toxic to rats and led to progressive hypochromic anemia with leukopenia and loss of weight The effects of linoleic acid were neutralized by administration of yeast According to Harrison,<sup>129</sup> rats made anemic by means of a milk diet responded slightly less well to iron and copper supplements when phytic acid was included in their diets This study was motivated by the observation, made previously, that phytic acid contributes to the production of rickets in rats by precipitating dietary calcium, and it was thought that a similar effect might be exerted on ingested iron

The concentration of copper in the blood of sheep and cows was determined by Beck<sup>130</sup> He found no absolute correlation between the values obtained and the development of anemia, but he states that anemia generally occurs if the copper level of the blood falls below 0.1 to 0.2 mg per liter for any length of time Sudden death, the "falling disease," is a not infrequent occurrence among cattle in certain areas of Australia Bennetts, Harley and Evans<sup>131</sup> have demonstrated quite conclusively that the death of these animals is due to severe anemia consequent on deficiency of copper Necropsy revealed atrophy and fibrosis of the heart similar to the starvation atrophy of the myocardium observed in human beings and death is attributed presumptively to either ventricular fibrillation or heart block It is suggested that copper may be necessary to the oxidation-reduction enzyme systems of bovine cells The tendency of the disorder to be manifest in the spring is believed to be due to the special stress and strain incident to this season, including rapid increase in weight, pregnancy and parturition

126 Brownlee, G., Bambridge, H. W., and Thorp, R. H. The Pharmacology of Iron in Parenteral Treatment, *Quart J Pharm & Pharmacol* **15** 148, 1942

127 Freeman, S., and Ivy, A. C. The Influence of Antacids upon Iron Retention by the Anemic Rat, *Am J Physiol* **137** 706, 1942

128 Gyorgy, P., Tomarelli, R., Ostergard, R. P., and Brown, J. B. Unsaturated Fatty Acids in Dietary Destruction of N, N-Dimethylaminoazobenzene (Butter Yellow) and in the Production of Anemia in Rats, *J Exper Med* **76** 413, 1942

129 Harrison, D. C. Phytic Acid in Anaemia, *Irish J M Sc*, 1942, no 201, p 540

130 Beck, A. B. Studies on Blood Copper of Sheep and Cows, *Australian J Exper Biol & M Sc* **19** 249, 1941

131 Bennetts, H. W., Harley, R., and Evans, S. T. Studies on Copper Deficiency of Cattle The Fatal Termination ("Falling Disease"), *Australian Vet J* **18** 50, 1942

Yoshikawa, Hahn and Bale<sup>121</sup> found that "following the ingestion of radioactive copper by the dog, the metal appears quickly in the plasma, the concentration reaching its peak in from two to five hours, after which it falls abruptly." The copper also appears in the circulating erythrocytes and the authors' data suggest that in dogs in which regeneration of erythrocytes is accelerated, because of previous hemorrhage the uptake of copper is somewhat more extensive than it is in nonanemic animals. This effect, however, may be due to greater absorption of copper by the newly formed red cells.

In stimulating the production of hemoglobin in anemic dogs Robschert-Robbins and Whipple<sup>122</sup> found the action of copper variable. In some instances copper enhanced the effect of iron, but in others regeneration was slowed. The diets were not deficient in copper and the hepatic and the splenic tissue of the anemic animals contained more of the metal than is present in the organs of normal dogs. The authors suggest that copper may exert an effect on enzyme complexes related to the production of globin and hemoglobin. When cobalt was administered to dogs, no tendency toward polycythemia was observed, but the ingestion of more than minimal amounts of cobalt exerted an inhibitory effect on the formation of hemoglobin in response to administration of iron.

Whipple and Robschert-Robbins<sup>123</sup> measured the hemoglobin-producing factors contained in human livers (obtained at necropsy from patients with various clinical conditions) by administering such material to dogs rendered anemic by repeated bleeding. It was found that in pernicious anemia in relapse and in aplastic anemia large stores of such factors were present. Following liver therapy the values in pernicious anemia were reduced. Conditions associated with "secondary" anemia were characterized by low or low normal values as determined by the production of hemoglobin. In polycythemia, hypoproteinemia, pregnancy with and without eclampsia, and lactation the values were abnormally low, whereas in hemochromatosis, erythroblastic anemia and hemolytic icterus the values were within or close to the normal range. A wide range of results was obtained in connection with leukemia. A general discussion of the role of amino acids in the formation of hemoglobin based largely on previously reported work, was published by Robschert-Robbins<sup>124</sup>.

Administration of a single therapeutic dose of copper containing the radioactive isotope,  $^{64}\text{Cu}$ , obtained by bombardment of nickel resulted in greater retention of the metal by copper-deficient rats than by iron-deficient animals, according to Schultze and Simmons<sup>125</sup>. In both groups only a small fraction of the copper fed was retained. Within twenty-four to forty-eight hours after ingestion the greatest deposition of copper was found in kidney, liver and marrow, in that order.

121 Yoshikawa, H., Hahn, P. F., and Bale, W. F. Red Cell and Plasma Radioactive Copper in Normal and Anemic Dogs, *J. Exper. Med.* **75** 489, 1942.

122 Robschert-Robbins, F. S., and Whipple, G. H. Copper and Cobalt Related Hemoglobin Production in Experimental Anemia, *J. Exper. Med.* **75** 481, 1942.

123 Whipple, G. H., and Robschert-Robbins, F. S. Hemoglobin Production Factors in the Human Liver. Anemias, Hypoproteinemia, Cirrhosis, Pigment Abnormalities and Pregnancy, *J. Exper. Med.* **76** 283, 1942.

124 Robschert-Robbins, F. S. Amino Acids in Hemoglobin Formation, *Federation Proc.* **1** 219, 1942.

125 Schultze, M. O., and Simmons, S. J. Use of Radioactive Copper in Studies on Nutritional Anemia of Rats. *J. Biol. Chem.* **142** 97, 1942.

histories of jaundice and anemia, who exhibited lasting erythroblastosis after splenectomy with no improvement in their anemia but with cessation of hemolytic crises. In all 3 cases the erythrocytes were of normal fragility, and in no case was spherocytosis observed. Five cases of hemolytic anemia, apparently not of the familial or spherocytic type, are reported by Sharpe and Tollman<sup>136</sup>. No cause for the hemolysis was discovered in any of these cases, and splenectomy was followed by slight improvement but no real cure. Hyperplasia of reticulum cells and phagocytosis of pigment were observed in the spleens, otherwise there were no definite pathologic changes.

A case of hemolytic anemia due to the presence of autoagglutinins and hemolysins is reported by Reisner and Kalkstein,<sup>137</sup> who point out that autoagglutinins are actually panagglutinins in that they act not only on the subject's red cells but on the erythrocytes of all other persons. The phenomenon is a true antibody reaction, and absorption of the antibody by the red cells can be demonstrated. The agglutination is usually accelerated by cold and retarded by heat, but in the case reported the reaction persisted in spite of warming to 37 C (98.6 F). The agglutinin could not be separated from the erythrocytes. Improvement followed splenectomy, and transfusions, which previously had been followed by severe hemolytic reactions, were tolerated after the operation, with resulting rise in the red cell count. The antibodies, however, persisted in the plasma, but presumably in insufficient concentration to produce an *in vivo* reaction. The death of this patient occurred on the ninth day after operation, apparently from exsanguination into the gastrointestinal tract. Necropsy was not performed.

The case of a man 41 years old with Gaucher's disease associated with severe hemolytic anemia is reported by Mandelbaum, Berger and Lederer.<sup>138</sup> The erythrocytes were not deficient in resistance to hypotonic salt solution, but occasional microspherocytes were seen. Splenectomy was followed by decided and continued improvement. Brewster and Wollenman<sup>139</sup> observed a patient with myeloid metaplasia of the spleen accompanied by acute hemolytic anemia. No extrinsic or intrinsic etiologic factors which might have accounted for the increased destruction of blood were discovered. There was increased fragility of the red cells, but the disease underwent exacerbation after splenectomy and terminated fatally. Pathologic evidence suggested that the spleen of this patient was an important blood-forming organ.

The literature on the familial anomaly of erythrocytes known as elliptocytosis is reviewed by Cooley.<sup>140</sup> Sixty-four families containing 246 affected persons have been reported. Of the affected ones, about 15 per cent were anemic. The fragility test was performed in two thirds of the cases, and decreased and normal resistance were observed in about equal numbers of cases. The author states that the erythrocytes do not acquire the characteristic oval form until they leave the reticulocyte stage of development. According to him, transfusion experiments indicate that cells of this type live only about half as long in the circulation as normal cells. Cooley's own patients with elliptocytosis all showed anemia,

136 Sharpe, J. C., and Tollman, J. P. Refractory Hemolytic Anemia. A Report of Five Cases in Which Treatment Was with Splenectomy, *Arch. Int. Med.* **70**: 11 (July) 1942.

137 Reisner, E. H., Jr., and Kalkstein, M. Autohemolytic Anemia with Auto-Agglutination. Improvement After Splenectomy, *Am. J. M. Sc.* **203**: 313, 1942.

138 Mandelbaum, H., Berger, L., and Lederer, M. Gaucher's Disease. A Case with Hemolytic Anemia and Marked Thrombopenia. Improvement After Removal of Spleen Weighing 6,822 Grams, *Ann. Int. Med.* **16**: 438, 1942.

139 Brewster, H. H., and Wollenman, O. J., Jr. Myeloid Metaplasia of the Spleen with Acute Hemolytic Anemia. Report of a Case, *New England J. Med.* **227**: 822, 1942.

140 Cooley, T. B. Elliptocytosis and Anemia, *Am. J. Dis. Child.* **64**: 190 (July) 1942.

## HEMOLYTIC AND ERYTHROBLASTIC ANEMIAS

*Congenital and Acquired Types*—The hemolytic syndromes are discussed, with a review of the recent literature on the subject, by Dameshek,<sup>132</sup> who gives the following classification of these disorders

- A Hemoglobinurias (exceedingly rapid hemolysis, with hemoglobinemia and hemoglobinuria)
  - 1 Paroxysmal cold
  - 2 Paroxysmal nocturnal
  - 3 March
  - 4 Favism
  - 5 Unclassified types
- B Hemolytic anemias
  - 1 Hereditary
    - a Spherocytic
    - b Target cell (Mediterranean)
    - c Sickle cell (African)
  - 2 Acquired (acute, subacute and chronic types)
    - a Chemical, including the sulfonamide drugs
    - b Immune body (hemolysins and agglutinins), including erythroblastosis foetalis
    - c Idiopathic, including hypersplenic types
    - d Symptomatic

A hemolytic index has been devised by Miller, Singer and Dameshek<sup>133</sup> which expresses the daily fecal output of urobilinogen per hundred grams of circulating hemoglobin. This value is obtained by the calculation

$$\frac{\text{Average (of 4 days) daily output of fecal urobilinogen (mg)} \times 100}{\text{Total hemoglobin (hemoglobin in Gm per 100 cc)} \times \frac{\text{total blood volume}}{100}}$$

Normal values for the hemolytic index range between 11.1 and 20.8. The values are increased in cases of hemolytic anemia, pernicious anemia, Cooley's anemia and, to some extent, Gaucher's disease. The values are below normal in cases of anemia due to deficiency of iron and cases of polycythemia and after splenectomy for any condition.

A family of which several members were afflicted with congenital hemolytic jaundice has been reported by Cooper<sup>134</sup> from Melbourne, Australia. The interesting feature of these patients was their similarity in many respects to patients with Cooley's erythroblastic anemia. The mongoloid facies was present, and there were extensive and characteristic changes in the bones of the vault of the skull. The author discusses the relationship of congenital hemolytic jaundice, sickle cell anemia and erythroblastic anemia. Three cases of chronic familial hemolytic anemia in which an erythroblastic reaction, manifest in the circulating blood, followed splenectomy are reported by Stransky and Regala.<sup>135</sup> One of the patients was a man of 23 years, in whom the erythroblastosis persisted for only a few days and was followed by the appearance of Howell-Jolly bodies and a rapid increase in erythrocytes. Two of the patients were girls 6 and 8 years old, with family

132 Dameshek, W. Hematology. Anemia, with Particular Reference to the Hemolytic Syndrome, New England J. Med. **226** 339, 1942.

133 Miller, E. B., Singer, K., and Dameshek, W. The Use of the Daily Fecal Output of Urobilinogen and the Hemolytic Index in the Measurement of Hemolysis, Arch. Int. Med. **70** 722 (Nov) 1942.

134 Cooper, E. L. Familial Acholuric Jaundice Associated with Bone Changes, Ann. Int. Med. **15** 858, 1941.

135 Stransky, E., and Regala, A. C. Erythroblastic Anemia Following Splenectomy in Cases of Chronic Familial Hemolytic Anemia, Am. J. Dis. Child. **63** 859 (May) 1942.

ranged from 19 months to 3½ years. The clinical picture consisted of a sudden onset of fever, hemoglobinuria, splenomegaly, anemia, jaundice and a rapid course terminating in death of 2 of the 4 children. There was no family history of a similar illness or of another form of blood dyscrasia in any of these patients. One of the patients who succumbed to the disease had had measles fifteen days previously. The authors discuss the causes of hemoglobinuria and hemoglobinemia as seen in infancy and state that these conditions may be associated with a variety of processes, including intoxications from chlorates, sulfanilamide and its derivatives, hydrogen sulfide, astringes, snake venoms, mushroom poisons, spider bites and severe burns. Among infectious agents responsible for acute hemolysis are mentioned scarlet fever, typhoid fever, diphtheria, pneumococcal infections, measles, erysipelas and malaria. Rather surprisingly, the authors fail to refer to sensitization to the protein of foods or inhalants as the mechanism responsible for this syndrome in some instances. Three other types of pathologic process are considered in the differential diagnosis of the cases reported. They are paroxysmal hemoglobinuria, acute hemolytic anemia of Lederer and the hemolytic crises of congenital hemolytic jaundice. The characteristic features of each of these conditions are described. The cases reported appear to fall in the second group, although the agents responsible for the acute hemolysis remain obscure.

With reference to a discussion of march hemoglobinuria, Comerford<sup>145</sup> in a letter to the editor of the *British Medical Journal* describes his own case observed in the 1880's after long distance running. He stated that his trainer regarded the passage of "port wine colored" urine as a common phenomenon among participants in this type of sport.

The behavior of erythrocytes obtained from normal subjects and from patients with a variety of clinical diseases in response to the hemolytic action of saponin, sodium carbonate, sodium oleate, ethyl alcohol and hypotonic sodium chloride solutions was determined by Wiczorowski and Fishback<sup>146</sup>. No changes of diagnostic value were found.

By intravenous injections of rattlesnake venom Bethell and Bleyl<sup>147</sup> were able to induce in dogs, rabbits and a monkey microspherocytosis, reticulocytosis, anemia and increased fragility of erythrocytes. After a number of these injections the animals became refractory to the action of the venom and the blood values returned to normal. The refractory period persisted for about two weeks after discontinuance of the injections. Splenectomy, although followed by morphologic changes in the circulating blood, did not affect the response of the animals to subsequent injections of venom.

A case of acute hemolytic anemia following administration of phenothiazine (anthelmintic) is reported by Johnstone<sup>148</sup>. He states that of 58 cases in which this drug was used, some form of toxic reaction severe enough to require treatment has occurred in 8. According to Collier and Allen,<sup>149</sup> phenothiazine in vitro

145 Comerford, B. H. March Haemoglobinuria, *Brit M J* **1** 774, 1942.

146 Wiczorowski, E., and Fishback, H. R. A Study of Type Hemolytic Reactions of Human Red Blood Cells in Disease, *J Lab & Clin Med* **27** 542, 1942.

147 Bethell, F. H., and Bleyl, K. The Production of Microspherocytosis of Red Cells and Hemolytic Anemia by the Injection of Rattlesnake *Crotalus atrox* Venom, *J Clin Investigation* **21** 641, 1942.

148 Johnstone, R. D. C. Acute Haemolytic Anaemia Following Phenothiazine Therapy, *Brit M J* **1** 259, 1942.

149 Collier, H. B., and Allen, D. E. The Haemolytic Action of Phenothiazine Derivatives, *Canad J Research* **20** 283, 1942.



which was to be expected, since they were referred to him for that reason and all were males, which was unexpected, since the trait is inherited as a mendelian dominant. Lasting relief from the anemia may follow blood transfusions.

The subject of Mediterranean anemia is reviewed by M. L. Goldhamer,<sup>141</sup> who reports 12 cases in a family of Italian origin, the patients representing three generations. Among them, features definitely indicative and features suggestive of Mediterranean anemia were observed. The presence of "target" cells and the increased resistance of the erythrocytes to hypotonic salt solution were cardinal characteristics. No form of therapy employed was of specific value, including administration of medicinal iron and liver preparations and maintenance on diets high in protein and vitamins.

Familial nonhemolytic jaundice, although not a disorder affecting the corpuscular elements of the blood, is properly considered in conjunction with the hemolytic anemias because of the likelihood of its being confused with them. An instance of this disease in an Irishman of 50 years is reported by Curry, Greenwalt and Tat.<sup>142</sup> The patient had been jaundiced since birth. He presented no evidence of disease of the liver or of the spleen and no anemia or reticulocytosis. The output of fecal urobilinogen was low, and the urinary urobilinogen was normal. Splenectomy, performed some years before, had been without effect on the jaundice. Biopsy of the liver revealed no pathologic change, and the results of tests of hepatic function were normal. The blood bilirubin level was elevated, the urine was free from bile, and the ingestion of sodium dehydrocholate was not followed by an increase in fecal urobilinogen. The patient's sister, aged 54, suffered from the same disorder.

The Marchiafava-Micheli syndrome is defined by Dameshek<sup>143</sup> as "chronic hemolytic jaundice with paroxysmal nocturnal hemoglobinuria and perpetual hemosiderinuria." Two cases are reported. One of the patients was a woman of 20 years, one of identical twins whose twin was not affected, and the other was a man of 23 years on whom splenectomy had been performed fourteen months before. This disease is characterized by either an abrupt or a gradual onset due to unknown factors and by the development of a specific and peculiar type of hemolytic antibody to which the red blood cells are sensitized. The cells are unusually susceptible to acid hemolysis. Greatly increased destruction of blood occurs with unusually marked and chiefly nocturnal hemoglobinemia and hemoglobinuria. There is also persistent hemosiderinuria, and both the hemoglobinemia and the hemosiderinuria are apparently mediated through the kidney. According to the author, this disease should be thought of in all cases of obscure hemolytic anemia, and in such cases the acid fragility test and an examination for hemosiderin should be done. The prognosis of paroxysmal nocturnal hemoglobinuria is unfavorable, and deposition of hemosiderin in the kidney frequently leads to impairment of renal function.

Four cases of hemoglobinuria occurring in boys, 3 of whom were of Jewish extraction, are reported by Acuña and Gambiassi.<sup>144</sup> The ages of the subjects

141 Goldhamer, M. L. Mediterranean Anemia in the Adult (A Family History Analysis), *Ohio State M. J.* **38** 321, 1942.

142 Curry, J. J., Greenwalt, T. J., and Tat, R. J. Familial Non-Hemolytic Jaundice. Report of a Case with Liver Biopsy, *New England J. Med.* **226** 909, 1942.

143 Dameshek, W. Paroxysmal Nocturnal Hemoglobinuria, Marchiafava-Micheli Syndrome, *Bull. New England M. Center* **4** 224, 1942.

144 Acuña, M., and Gambiassi, A. C. A proposito de algunos casos de hemoglobinuria con síndrome anemioictérico agudo, grave (anemia hemolítica, de Lederer), *Arch. argent. de pediat.* **17** 421, 1942.

lobar pneumonia showed acute hemolytic anemia Hipsley<sup>154</sup> reports a case of severe hemolytic anemia in a girl of 3 years who received only 3 grains (0.19 Gm) of sulfapyridine in treatment of acute tonsillitis and whose erythrocyte count twenty-four hours later was 1,430,000 per cubic millimeter. The patient recovered following transfusion therapy.

Foy and Lewis<sup>155</sup> studied the effect of blood transfusion in the hemolysis associated with blackwater fever and that caused by the administration of sulfanilamide or its derivatives. In neither of these hemolytic states did they find any evidence that blood transfusions aggravate the destruction of erythrocytes.

The effect of promin (a glucoside derivative of 4,4-diaminodiphenyl sulfone) on the blood was investigated by Hall and his associates<sup>156</sup>. This compound was administered in 70 cases of tuberculosis. In 64 of the cases the disease involved the lungs, and in the remainder it was a meningeal, renal or bone infection. The drug was usually given by mouth and thus administered it was much more toxic with respect to incidence and severity of hemolytic anemia than when given by a parenteral route. After daily doses of 3.2 Gm had been given for a period of eight to ten days, hemolysis usually developed, accompanied by anemia, leukocytosis and thrombocytosis. When the doses given during the initial period of administration were relatively small, "tolerance" was sometimes acquired, which was interpreted as a state in which regeneration of erythrocytes was stimulated to such an extent that anemia either failed to develop or was minimal. On discontinuance of the medication the blood values returned promptly to normal, without evidence of residual harmful effects on the hemopoietic system. One of the patients had extremely severe anemia, with an erythrocyte count of 900,000 per cubic millimeter, after 1.6 Gm of promin had been administered daily for three days. When the administration of the drug was discontinued, recovery was spontaneous.

*Erythroblastosis Foetalis and Icterus Gravis Neonatorum*—In a pathologic study of erythroblastosis Javert<sup>157</sup> classifies 47 cases observed by him into five groups: (1) cases with hydrops, 16, (2) cases with icterus, 22, (3) cases with anemia, 3, (4) cases with hemorrhagic diathesis, 3, (5) cases without hydrops, icterus, anemia or hemorrhagic diathesis, 3. The mortality in these groups was, respectively, 100, 54, 33, 33 and 100 per cent. The total incidence of erythroblastosis was 1 case to every 438 newborn infants, and the condition was held responsible for 3.2 per cent of all fetal deaths. The author believes that dysfunction of the fetal liver plays an important part in the genesis of this disorder.

Five infants in whom erythroblastosis was the cause of death are the subject of an article by Follis, Jackson and Carnes<sup>158</sup>. Hydrops foetalis was present in 3 infants and icterus gravis with hemorrhagic diathesis in a fourth, the fifth child appeared to be normal, but at necropsy enlargement of the liver and of the spleen, with active erythropoiesis in these organs and in the kidneys, was observed. Particular emphasis was placed on the changes in the bones, of which the most

154 Hipsley, P. L. Acute Hemolytic Anaemia Following Sulfonamide Therapy, *M. J. Australia* **1** 565, 1942.

155 Foy, H., and Lewis, E. G. Blood Transfusion in Blackwater Fever and Haemolytic Anaemias Following Sulphonamide Therapy, *Bull. War Med.* **2** 490, 1942.

156 Hall, B. E., Pfuetze, K., Hinshaw, H. C., and Feldman, W. H. Effect of Promin on Blood of Patients with Tuberculosis. Preliminary Report, *Proc. Staff Meet., Mayo Clin.* **17** 24, 1942.

157 Javert, C. T. Erythroblastosis Neonatorum. An Obstetrical-Pathological Study of Forty-Seven Cases, *Surg., Gynec. & Obst.* **74** 1, 1942.

158 Follis, R. H., Jr., Jackson, D., and Carnes, W. H. Skeletal Changes Associated with Erythroblastosis Foetalis, *J. Pediat.* **21** 80, 1942.

appears to act as an accelerator of hemolysis induced by either saponin or lysolecithin

*Hemolytic Anemia Produced by Sulfanilamide and Its Derivatives*—An instance of acute hemolytic anemia occurring during administration of sulfapyridine (2-[paraaminobenzenesulfonamido]-pyridine) is reported by Trier,<sup>150</sup> who analyzes the data supplied by about 90 cases of anemia attributed to the action of sulfanilamide and its derivatives, including sulfapyridine and sulfathiazole (2-[paraaminobenzenesulfonamido]-thiazole). Three fatalities are included in this series. The anemia is characterized by an abrupt onset, usually occurring between the third and the fifth day of administration of the drug, with rapid fall in the erythrocyte and hemoglobin values, jaundice, urobilinuria, leukocytosis and reticulocytosis. In the cases in which the intoxication is severe, hemoglobinemia, hemoglobinuria and enlargement of the liver are observed. The majority of persons who have had acute anemia from this cause will show recurrence on readministration of the same drug or another member of the sulfanilamide group.

Hendricks<sup>151</sup> reports that anemia of varying severity developed in 40 per cent of 433 patients who received one or more of the sulfanilamide derivatives. The incidence of anemia was about the same with sulfanilamide, sulfapyridine and sulfathiazole but was increased when more than one of these drugs were employed. Infants and children proved to be more susceptible than adults. Acute hemolytic anemia developed in 4.3 per cent of the patients, and was caused by each of the drugs employed, but most frequently by sulfanilamide or mixed therapy. The incidence of hemolytic anemia was almost three times as great in Negroes as in Caucasians. The onset of anemia was sometimes delayed for as long as ten to twelve days after the institution of therapy, and it did not appear to be dependent on the duration of treatment or on the concentration of the responsible drug in the blood.

A case of acute hemolytic anemia following administration of sulfathiazole is reported by Rothstein and Cohen.<sup>152</sup> Their patient, a man of 45 years, had lobar pneumonia caused by pneumococcus type VII. On the sixteenth day of the administration of the drug, hemoglobinuria, severe hemolytic anemia, a leukemoid reaction with a leukocyte count of 67,000 per cubic millimeter, autoagglutination of red cells, toxic hepatitis and signs of renal damage developed. Arrest of the hemolytic process and recovery from the anemia were relatively rapid following the institution of blood transfusion therapy, but evidence of hepatic and renal damage persisted for a long time. Bunim and Israel<sup>153</sup> report the case of a man of 38 years who received 18 Gm of sulfathiazole over a period of eight days in treatment of cellulitis of the foot before development of jaundice, hemoglobinemia, hemoglobinuria, azotemia and impairment of renal function. Prompt recovery occurred after discontinuance of the drug and administration of blood by transfusion. Another case, reported by the same authors, was that of a man aged 52 who after receiving 16 Gm of sulfathiazole during four days in treatment of

150 Trier, M. Acute Hemolytic Anemia Developing During Therapy with Substances Belonging to the Sulfanilamide Group. Survey and Report of Case, *Acta med Scandinav* **108** 117, 1941.

151 Hendricks, C. B. Sulfonamide Compounds. Blood Changes Therefrom, *California & West Med* **56** 253, 1942.

152 Rothstein, I., and Cohen, S. Acute Hemolytic Anemia, Autoagglutination, Toxic Hepatitis and Renal Damage Following Sulfathiazole Therapy. Case Report, *Ann Int Med* **16** 152, 1942.

153 Bunim, J. J., and Israel, M. Acute Hemolytic Anemia Caused by Sulfathiazole. *Ann Int Med* **16** 333, 1942.

of these infants was studied with reference to the presence of Rh agglutinin in the erythrocytes. Of 50 mothers of infants with the pathologic diagnosis of erythroblastosis foetalis, 86 per cent were found to have blood cells negative for Rh antigen and 14 per cent blood cells positive for this antigen, whereas, of 31 mothers of infants who did not have pathologic evidence of erythroblastosis, 15.5 per cent had blood cells negative for Rh antigen and the remainder blood cells positive for this antigen. Two infants with erythroblastosis foetalis were shown to have Rh negative erythrocytes and 1 father of an affected infant to have Rh negative erythrocytes.

The isoimmunization theory of erythroblastosis foetalis postulates the passage of fetal erythrocytes across the placental barrier into the maternal blood stream. Since this is not a physiologic process, the presence of placental defects as well as an immunologic reaction between maternal antibody and fetal red cells must be assumed in all cases of erythroblastosis. Burnham<sup>165</sup> submits the hypothesis that breaks in the integrity of the fetal circulation through the placenta are dependent on maternal deficiency of vitamin C, and that, therefore, the administration of vitamin C during pregnancy may be of prophylactic value in cases in which there is a history of erythroblastosis or unexplained fetal deaths. The author presents some clinical evidence in support of this theory.

Differences in specificity and in sensitivity between human anti-Rh serums were noted by Davidsohn and Toharsky<sup>166</sup>. They advocate the use of at least three such serums in testing for the Rh factor. There are also antigenic variations of the Rh factors from human sources, and definite differences in this respect between man and *Macacus rhesus* monkeys with Rh-positive tests. Taylor and his associates<sup>167</sup> found that the weakly Rh-positive erythrocytes failed to agglutinate with undiluted anti-Rh serum obtained from the mother of an infant who died of erythroblastosis, but that agglutination took place when the serum was suitably diluted. They therefore advocate that a titration method be used before reaching the conclusion that anti-Rh factor is not present in a serum.

A discussion of the role of Rh isoimmunization in the genesis of erythroblastosis foetalis and certain transfusion reactions is given by Aagaard,<sup>168</sup> who reports 2 such reactions in women recipients. In an article on hemolytic transfusion reactions, Wiener<sup>169</sup> reports the case of a 16 month old child in whom serum autoagglutinins were demonstrated which retained their activity at refrigerator, room or body temperature. According to the author, a similar case has been observed by Kracke but has not been reported.

Franklin<sup>170</sup> reports the case of an infant in whom sulfhemoglobinemia developed spontaneously about twelve days after birth and was followed by severe anemia without erythroblastosis, jaundice or splenomegaly. The sulfhemoglobinemia and anemia responded to blood transfusions, but the child subsequently died of emaciation and bronchopneumonia.

<sup>165</sup> Burnham, L. Vitamin C Deficiency as a Possible Factor in the Pathogenesis of Erythroblastosis Foetalis, *Am J Obst & Gynec* **44** 920, 1942.

<sup>166</sup> Davidsohn, I., and Toharsky, B. The Rh Blood Factor. An Antigenic Analysis, *Am J Clin Path* **12** 434, 1943.

<sup>167</sup> Taylor, G. L., and others. Optimal Proportions of Antigen and Antibody in Tests for Rh Antibodies, *Brit M J* **2** 572, 1942.

<sup>168</sup> Aagaard, G. M. Transfusion Reactions and Erythroblastosis Foetalis Caused by the Rh Factor, *Minnesota Med* **25** 267, 1942.

<sup>169</sup> Wiener, A. S. Hemolytic Transfusion Reactions. Diagnosis with Special Reference to the Method of Differential Agglutination, *Am J Clin Path* **12** 189, 1942.

<sup>170</sup> Franklin, A. W. Sulphæmoglobin (cyth) æmia and Anæmia Neonatorum, *Proc Roy Soc Med* **35** 686, 1942.

striking was a marked increase of density. In all the cases serologic tests for syphilis were negative. Henderson<sup>159</sup> reports 4 cases of severe erythroblastosis foetalis with intrauterine death of the fetus. The findings in this disease and in congenital syphilis are compared. The author points out that the latter condition is likely to die out with successive pregnancies, whereas erythroblastosis tends to become more severe. Attention is drawn to the characteristic change of the placenta in erythroblastosis, consisting in persistence to term of Langhans' layer of cells in the chorionic villi.

In a letter to the editor of the *British Medical Journal* Levy<sup>160</sup> mentions polyostatic fibrous dysplasia, or Albright's syndrome, as a possible sequel to erythroblastosis foetalis, which he prefers to term "hemolytic disease of the new-born," since neither anemia nor erythroblastosis may be conspicuous. Dizygotic twins suffering with erythroblastosis are reported by Buhler, Seely and McCormick.<sup>161</sup> Their mother was 31 years old. She had been gravid eight times and had been delivered of 5 children, 3 of whom were living. There had been two abortions. The twins died, and necropsies confirmed the diagnosis. The first twin was a stillborn girl. No tests for Rh agglutinin in her blood were made. The second a boy, lived for sixty hours, and his erythrocytes were shown to be Rh positive. The father's erythrocytes were also Rh positive, the mother's were Rh negative.

The subject of isoimmunization with reference to erythroblastosis foetalis and other manifestations is discussed by Levine.<sup>162</sup> He points out that, unlike the Rh antigen, A and B factors are widespread throughout the tissues, and that consequently isoimmunization of the mother to A and B agglutinins of the fetus with subsequent action of the anti-A and anti-B factors within the fetal tissues may be an important cause of fetal mortality. The author refers to the probable role of isoimmunization in animals and states that concepts of this type of reaction have been formulated and discussed in the older literature but that until now the data have been inconclusive. He considers that the subject merits reopening.

Forty-eight mothers of infants suffering with erythroblastosis were studied by Boorman, Dodd and Mollison.<sup>163</sup> with reference to the Rh factor. The erythrocytes of all of the affected babies were Rh positive, the erythrocytes of 46 of the mothers were Rh negative, and in the blood of 44 of the mothers Rh agglutinin was demonstrated. In the 4 mothers without Rh antibodies other group differences were found, for instance, the maternal blood belonged to group O and the fetal blood to group A. In the blood of both members of identical twins Rh agglutinin was detected within twenty-four hours after birth. The authors submit evidence indicating that some cases of "physiological" icterus of the newborn are really instances of mild icterus gravis neonatorum, since weak Rh agglutinin was demonstrated in the blood of some mothers of infants with "physiological" jaundice.

The pathologic examination of 3,000 fetuses and newborn infants revealed erythroblastosis in 120, according to Potter.<sup>164</sup> The blood of 81 of the mothers

159 Henderson, J. L. Erythroblastosis or Congenital Syphilis? Observations on Erythroblastosis and Its Differential Diagnosis from Congenital Syphilis, *J. Obst. & Gynaec. Brit. Emp.* **49** 499, 1942.

160 Levy, H. Erythroblastosis Foetalis, *Brit. M. J.* **2** 738, 1942.

161 Buhler, V. B., Seely, C. W., and McCormick, C., Jr. Erythroblastosis Foetalis in Dizygotic Twins, *J. Missouri M. A.* **39** 106, 1942.

162 Levine, P. Erythroblastosis Foetalis and Other Manifestations of Isoimmunization, *West. J. Surg.* **50** 468, 1942.

163 Boorman, K. E., Dodd, B. E., and Mollison, P. L. The Clinical Significance of the Rh Factor, *Brit. M. J.* **2** 535 and 569, 1942.

164 Potter, E. L. The Rh Factor in Erythroblastosis, *Am. J. Dis. Child.* **64** 957 (Nov.) 1942.

believed to be due to long-standing severe anemia, and congestive failure, not responding to digitalis therapy, is common only in the terminal stages of the disease

The varied types of cutaneous manifestations occurring in sickle cell anemia are described by McGavack and Nussbaum<sup>175</sup> Of 214 cases observed by the authors, jaundice was present in 204, and ulcers of the extremities, usually on the medial aspect of the leg above the ankle, were found in 55 Other changes included areas of vitiligo, with surrounding zones of increased pigmentation, and subcutaneous nodules which bore a resemblance to the lesions of erythema nodosum

During a five year period, ending on Nov 1, 1941, 57,455 Negro males were admitted to the Charity Hospital, New Orleans, according to Getzoff<sup>176</sup> A diagnosis of sickle cell anemia was made for 65 of them Sickle cell anemia was not observed in any white patient In this five year period priapism was noted in 11 Negro males, and in 3 this complication occurred with sickle cell anemia Priapism in these 3 is explained as due to venous stasis resulting in increased sickling and thrombosis

The first case of sickle cell anemia to be described in the medical literature of Argentina was reported by Zerbino, Volpe and Norbis<sup>177</sup> The patient was a 2½ year old Mulatto girl, and the disease was entirely characteristic

*Erythroblastic (Cooley's) Anemia*—The case of a young man 19 years old of Sicilian origin, with erythroblastic anemia is reported by Smith<sup>178</sup> The patient had been under observation since the age of 4 and presented all the clinical, hematologic and roentgenologic features of the disease In childhood he required blood transfusions, but his development to adult life was normal, and he participated in all forms of activity and exhibited no special susceptibility to infections One sibling also had Cooley's anemia, and the red cells of another sibling and both parents showed abnormalities, including varying numbers of hypochromic macrocytes and basophilic stippling The erythrocytes of the father and the brother showed increased resistance to hypotonic solutions of sodium chloride, together with abnormal thinness Such morphologic changes in the erythrocytes indicate, in the author's opinion, that the relatives of their patient were carriers of this disorder This case was also reported, in less detail, in 1941

McIntosh and Wood,<sup>179</sup> explaining the development of erythroblastic anemia, exclude on the basis of improbability most types of genetic factors They believe that the simultaneous inheritance of two dominant and nonlethal genes is compatible with the observed clinical evidence of a 1/3 incidence of the disease among siblings

(To Be Continued)

175 McGavack, T H, and Nussbaum, C C Skin Manifestations of Sickle Cell Anemia, *Urol & Cutan Rev* **46** 194, 1942

176 Getzoff, P L Priapism and Sickle Cell Anemia A Report of Three Cases, *J Urol* **48** 407, 1942

177 Zerbino, V, Volpe, A, and Norbis, A Anemia a células falciformes en una mulatita, *Arch argent de pediat* **17** 303, 1942

178 Smith, C H Mediterranean (Cooley's) Anemia in a Youth of Nineteen Years Observed Since Early Childhood Familial Aspects and Hematologic Features of the "Carrier" or Asymptomatic Case, *J Pediat* **20** 370, 1942

179 McIntosh, R, and Wood, C L An Inquiry into the Genetic Factor in Cooley's Anemia, *Am J Dis Child* **64** 192 (July) 1942

*Sickle Cell Anemia*—Two cases of sickle cell anemia in the white race are reported by Morrison, Samwick and Landsberg<sup>171</sup> The ancestors of the patients, who were unrelated, were Italian, and their parents were born in Italy and emigrated to the United States The sickling trait was detected, in each instance, by means of material obtained by splenic puncture Subsequently, the trait was demonstrated in members of three generations of both families

A detailed description of the changes in the brain occurring as the result of sickle cell anemia has been published by Wertham, Mitchell and Angrist<sup>172</sup> Five unselected fatal cases of the disease provided the material for this study The presence of sickle cells in the tissues was the most conspicuous neuropathic feature Small necrotic and necrobiotic lesions on a vascular basis were observed, diffusely distributed, but most numerous in the zone between the cortex and the subcortical white matter In all cases there were hypertrophy and hyperplasia of endothelial and adventitial cells lining the smaller blood vessels, with siderotic pigment appearing both in the adventitial cells and in the intra-adventitial spaces Generalized hyperemia and constriction of blood vessels were conspicuous Small hemorrhages and extravasations were prevalent, and larger vascular lesions of uncharacteristic type including softening and thrombosis, were seen Intravascular lipid material, with fat embolism of the capillaries and precapillaries, was observed, together with focal and diffuse changes in the nerve cells in the cortical and subcortical gray structures In addition, focal areas of demyelination were present in the spinal cord, similar to those seen in subacute combined degeneration

The case of a Negro woman aged 20 who died with massive cerebral necrosis on the basis of sickle cell anemia is reported by Connell<sup>173</sup> According to the author, this is the fifth case to be reported He states that his patient presented the most extensive cerebral necrosis due to sickle cell anemia which has so far been described Ultimately, the entire left hemisphere became involved, although in view of the history the onset and progress of the condition appeared to have been gradual The author emphasizes that in this disease it is not anemia but thrombosis which constitutes the most important pathologic process Such vascular lesions may occur in any organ but are especially common in those with a terminal circulation

It is well known that cardiac enlargement is a usual finding in patients with sickle cell anemia Klinefelter<sup>174</sup> confirms this observation on the basis of a study of 12 cases of the disease including postmortem examination in 11 instances In all of the patients the heart was diffusely enlarged Usually both a systolic and a diastolic murmur were present, together with a third sound heard at the apex and accentuation of the second pulmonic sound, with a systolic murmur at the base The author discusses the similarities between rheumatic fever and sickle cell anemia and points out that in the latter condition pain is not confined to the joints and that the therapeutic response to administration of salicylates is not striking He states that necropsy has never confirmed the concomitance of rheumatic fever and sickle cell anemia The cardiac changes in the latter disease are

171 Morrison, M., Samwick, A. A., and Landsberg, E. Sickle Cell Anemia in the White Race. Report of Two Cases with Diagnosis by Splenic Puncture, *Am J Dis Child* **64** 881 (Nov.) 1942

172 Wertham, F., Mitchell, N., and Angrist, A. The Brain in Sickle Cell Anemia *Arch Neurol & Psychiat* **47** 752 (May) 1942

173 Connell, J. H. Cerebral Necrosis in Sickle Cell Disease, *J A M A* **118** 893 (March 14) 1942

174 Klinefelter, H. F. The Heart in Sickle Cell Anemia, *Am J M Sc* **203** 34, 1942

## Book Reviews

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**Osler's Principles and Practice of Medicine** By Henry A. Christian, A.M., M.D., LL.D., Hon. Sc.D., Hon. F.R.C.P. (Canada), F.A.C.P. Hersey Professor of the Theory and Practice of Physic, Emeritus, Harvard University, Physician in Chief, Emeritus, Peter Bent Brigham Hospital, Visiting Physician, Beth Israel Hospital, Boston. Pp. 1475. Cloth. Price, \$9.50. New York: D. Appleton-Century Company, Inc., 1942.

This is the fourteenth edition of this book and celebrates its fiftieth birthday. A comparison of the first edition with the present one has shown that the original work contains 1,079 pages and the present edition 1,475. It is a tribute to the present author that he has been able to bring the work up to date with the addition of these relatively few pages. One must remember that vitamins, hormones, the types of cardiac arrhythmia and even diphtheria antitoxin, to say nothing of sulfanilamide and its derivatives, were still to be introduced into medicine in 1892. The specific infectious diseases of the first edition have been subdivided into groups according to causative agents: bacteria, viruses, rickettsias, bartonellas, fungi and protozoa. None of the "infectious diseases of doubtful nature" of the first edition are so listed in the present one. These have all been fitted into the proper places. There is, however, a bigger and better list to supply the deficit. These represent only a few of the many changes. Even so, it is surprising how much of the original work could be written almost unchanged into the present one.

The book is, of course, excellent. The background plus the present author would insure this. Much of the material has been rearranged. Among the infectious diseases, typhoid has yielded first place to pneumonia. It is rather surprising that the author has given first place in the book to psychosomatic medicine and functional diseases of the nervous system. There can be no question of the increasing incidence of these disorders, but one wonders whether they should occupy first place in the mind of the student or even first place in a textbook. Perhaps it is a trend of the times.

**Brucellosis in Man and Animals** By I. F. Huddleson, D.V.M., Research Professor in Bacteriology, Michigan State College, A. V. Hardy, M.D., Associate Professor of Epidemiology, Columbia University Medical School, J. E. Debono, M.D., Professor of Pharmacology and Therapeutics, Royal University of Malta, Ward Giltner, D.V.M., Professor of Bacteriology, Michigan State College. Revised edition. Price \$3.50. Pp. xv + 379, with 42 illustrations. New York: The Commonwealth Fund, 1943.

The ARCHIVES OF INTERNAL MEDICINE has already bowed in a complimentary manner to what might be termed the grandfather and father of this book. For the first edition appeared as a short monograph in 1934 and received a pleasant notice (ARCH. INT. MED. 54:658 [Oct.] 1934), and the second edition, which came out in 1940 as a larger and more comprehensive study, also received a flattering review (ibid. 66:1358 [Dec.] 1940).

The third edition continues to live up to the standards of its forebears. As one reads the book now, one is struck with the fact that it has been put together by a competent team of experts, each member of which knows so well what he writes that the final result is admirable. Brucellosis is so discussed that the bacteriologist, the pathologist, the veterinarian, the public health official and the clinician can find in the volume what he wishes to learn.

The first edition included a bibliography of one hundred and thirty-eight titles. The third edition refers to four hundred and eighty-five articles. Thus the third edition keeps abreast of the times and continues to make the book an effective aid in helping to control a disease which is becoming increasingly important over the entire world.

**A Manual of Pulmonary Tuberculosis and an Atlas of Thoracic Roentgenology** By D. O. N. Lindberg, M.D., Lecturer on Tuberculosis, University of Iowa Medical College. Price \$6.50. Pp. xv + 233, with 199 illustrations. Springfield, Ill.: Charles C. Thomas, Publisher, 1943.

The author has divided this book into two parts. The first is a seventy-two page monograph on pulmonary tuberculosis, the second is an atlas of thoracic roentgenology. Each is written briefly and clearly.

At the outset, in the first part of the book, pulmonary tuberculosis is discussed in orthodox fashion by a short description of its pathology and methods of diagnosis. Then



## Correspondence

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### A RENAL CONCENTRATION TEST USING SOLUTION OF PITUITARY

*To the Editor* —I read with great interest the excellent paper of Lieutenant Harry C Wall entitled "A Renal Concentration Test Using Solution of Pituitary" in the April 1943 issue of the ARCHIVES OF INTERNAL MEDICINE

I am sure that you and the author will be interested in the fact that in 1921 I published a paper, 'Pituitrin zur Nierenfunktionsprüfung' (*Med Klin* **17** 871 [July 17] 1921)

As the title implies, I suggested the use of solution of pituitary instead of a period of thirst in order to determine the ability of the kidneys to produce a concentrated urine. I reported 3 cases of impaired renal function in which tests done by means of solution of pituitary gave the same results as tests of concentration done by means of a period of thirst. I am sorry that I have no reprint to send you.

F BRUNN M.D., New York

**Dictionary of Bio-Chemistry and Related Subjects** Edited by W M Melisoff, Professor of Bio-Chemistry, Brooklyn Polytechnic Institute Price \$7 50 Pp 579 New York Philosophical Library, Inc, 1943

Nowadays the internist hears a good deal of a new kind of language which is likely to be all Greek to him but which his friends who are interested in chemistry or physics speak with fluent glibness. Thus a lexicon of such a new language is bound to be helpful to the casual listener. One can learn a good deal of any tongue by the diligent translation of new words or phrases into one's own vocabulary.

The editors of this dictionary have completed a task for which many members of the medical profession will be grateful. The editorial board is comprised chiefly of a group of distinguished biochemists who have added to their roster an occasional clinician. Between them they have been ingenious enough to complete a readable dictionary, defining in a readily understandable way many of the new words which they use so fluently in connection with their daily work. Usually the various definitions for each word take up a few lines, but occasionally a short article is necessary to explain a word whose meaning cannot be simplified. In such instances a useful bibliography is appended to the article.

The preface states that the dictionary is a pioneering effort in an entirely new field. It is, in fact, sort of a cross between an ordinary dictionary and an encyclopedia. All medical students and a great many physicians will appreciate having placed at their disposal such a useful tool.

**Civilian Health in Wartime** Francis R Dieuaide, M.D., Associate Professor of Medicine Harvard Medical School and Member of the Staff of the Massachusetts General Hospital Price, \$2 50 Cambridge, Mass Harvard University Press, 1942

The author presents a well written book covering phases of health on which the war will exert an influence. In the first chapter he considers the effect of war on the civilian population and on its mode of life. In the subsequent chapters he discusses these problems in detail, outlining the effects and the methods of prevention. The chapters on nutrition are especially good and timely. A chapter on "The Aging and the Aged" offers an optimistic note for this group. In the final chapters he emphasizes the result of war stress on civilian mental health and morale and discusses how these may be maintained. He discusses these problems from the standpoint of the physician, with a fine interest in public health and social welfare.

The reviewer believes that "Civilian Health in Wartime" will not appeal to the general reader because of its technicalities, but feels that it is worth while reading for the physician, the medical student, the social worker and students in sociology. It would serve well as required reading for any student of social trends.

The entire substance of the book is well handled. Particularly commendable is the author's modern outlook concerning not only medical care but other needs of the community.

**La urobilina en el estado normal y patológico** By Marcello Royer Second edition Buenos Aires El Ateneo, 1943

Well printed, this small volume contains review and original work covering the physiology and pathology of urobilin. Brief, well organized for reference, interesting in the original experiments and studies, the book, alas, definitely puts an end to the hopes of both investigators in clinical laboratories and clinicians that urobilin, so tempting to test for, is of any practical clinical diagnostic value.

**Medico-Legal Blood Group Determination** By David Harley Price 2s 6d Pp 119, with 13 figures London William Heinemann Medical Books, Inc, New York Grune & Stratton, Inc, 1943

This little book covers in a thorough manner the medicolegal aspects of determinations of blood group, especially with reference to questions of disputed paternity, blood stains, etc. Much of the material is highly technical, and it becomes evident that the more esoteric problem of blood typing usually must be dealt with by an expert. There are a bibliography, an index and many illustrative charts and figures.

comes a chapter which is of chief interest to the reader who is not an expert roentgenologist. For here is described roentgenologic technic and interpretation of roentgenograms of the chest. Two excellent chapters on the treatment of tuberculosis follow, the first dealing with methods of medical treatment and the second with modern ways of attacking tuberculosis by surgical measures. Finally, a brief chapter discusses control of the disease. The text is accompanied with forty-four excellent charts and photographs which illustrate the pathologic changes in tuberculosis, its method of spread and the mechanical implements used in its diagnosis and treatment. The net result is pleasing.

The second part of the book is an atlas of one hundred and forty-five roentgenograms chosen to illustrate how pulmonary tuberculosis in different forms appears on a roentgenogram and how it can be differentiated from some of the more common intrathoracic lesions that so often puzzle every internist. The significance and high points of each illustration are explained in a few words. The roentgenograms have been reproduced with a notable degree of success, so that little in the way of fine detail has been lost.

The total result is a helpful book. Its author deserves hearty congratulations. He has condensed into a surprisingly small volume a comprehensive manual of pulmonary tuberculosis which will be appreciated by medical students, by practitioners and by specialists in the field of pulmonary disease.

**Clinical Roentgenology of the Cardiovascular System** By Hugo Roesler, M.D., F.A.C.P., Associate Professor of Roentgenology and Cardiologist, Department of Medicine, Temple University School of Medicine, Cardiologist, Temple University Hospital, Philadelphia. Second edition. Price \$7.50. Pp 480, with 337 figures. Springfield, Ill. Charles C Thomas, Publisher, 1943.

This monograph is an authoritative presentation of the physiology and pathology of the cardiovascular system. It is viewed from the roentgenologic aspect by a cardiologist with a wealth of clinical experience and material.

The text describes technic, apparatus and findings of the most acceptable methods in roentgenoscopy, fluoroscopy, orthodiagraphy, roentgenography, cinematography, kymography and vasography. Interpretations include etiologic factors and differential diagnoses.

The organization of the subjects is such that reference may readily be made to detail of technical methods, correlation from different aspects, interrelationships of heart, vessels, lungs, diaphragm and the thoracic cage in the dynamics of blood flow and respiration, and discussions of changes in cardiac, concomitant pulmonary, aortic, pericardial, pulmonic and peripheral vascular diseases. Each chapter is replete with excellent illustrations, diagrams, electrocardiograms, medical histories, clinical courses, in many instances covering a long course of years, postmortem data and an extensive bibliography.

The book is invaluable in adding knowledge to those on whom lies the task of diagnosis of cardiovascular diseases.

**Blood Groups and Transfusion** By A. S. Wiener, M.D., Serologist and Bacteriologist in the office of the Chief Medical Examiner of New York City. Third Edition. Price \$7.50. Pp xiv + 438 with 106 tables and 69 illustrations. Springfield, Ill. Charles C Thomas, Publisher, 1943.

The first two editions of this book have already received compliments from the *ARCHIVES OF INTERNAL MEDICINE*. The first edition was reviewed in the issue of December 1935 (56:1298 [Dec.] 1935) and the second in the issue of December 1940 (66:1360 [Dec.] 1940). The third edition, too, without question deserves praise.

As was said in the review of the first edition, the book brings together practically everything that is known about blood groups. It does this in a readable, scholarly way. To make the subject matter more graphic and readily understandable, it has many good illustrations.

The third edition discusses the Rh factor and its role in erythroblastosis foetalis and transfusion of stored blood and blood substitutes—two subjects not mentioned in the first edition. The book is almost exactly twice as large as it was in the beginning, which seems to indicate that much has been added to the knowledge of blood in eight years. Naturally, the third edition is a better and more comprehensive volume than either of its predecessors, but it continues to hew to the old line in a satisfactory manner.

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